The American Journal of Medicine

April 1953

The American Journal of Medicine

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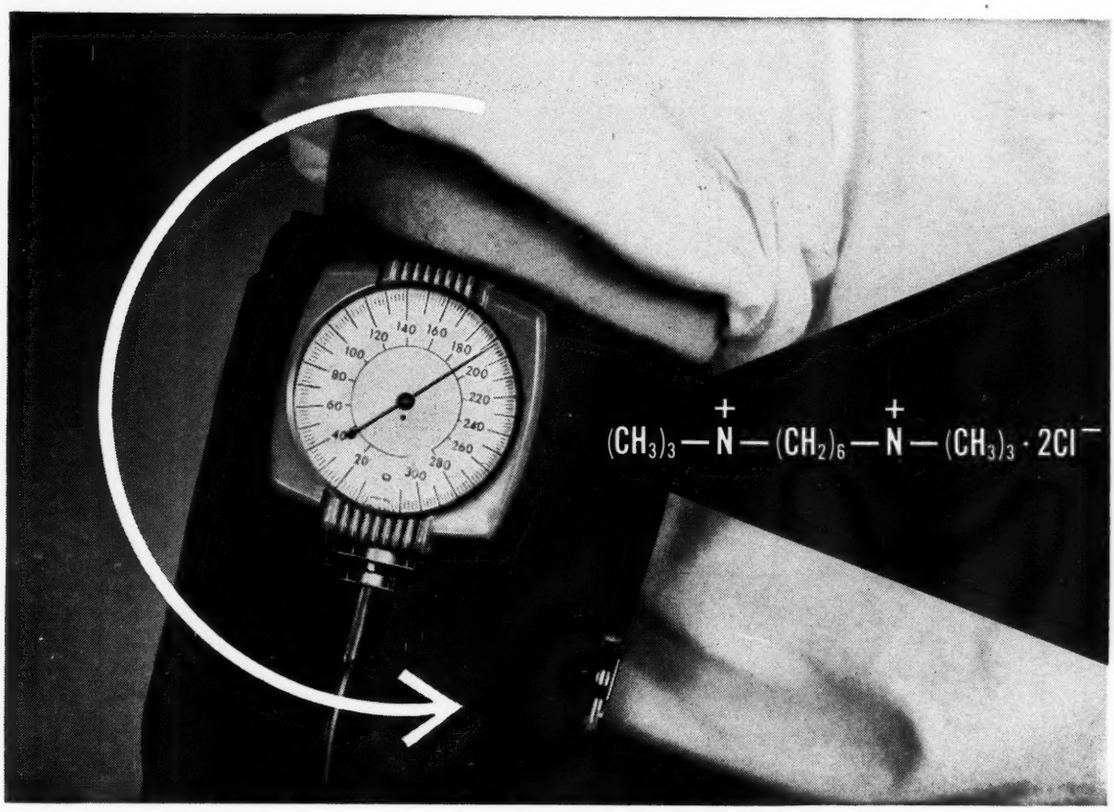

to lower a hypertensive's blood pressure

It is desirable to

1. reduce blood pressure to near-normal or normal levels
2. alleviate hypertensive manifestations
3. improve patient's condition even if blood pressure is not markedly altered.

These objectives are now attainable with Methium —an "orally effective ganglionic blocking agent."[1] The clinically significant drop in blood pressure usually results in disappearance of subjective symptoms such as headache, dizziness, fatigue, palpitation.

Methium is indicated specifically in cases of severe hypertension unresponsive to the conventional therapy of bed rest and sedatives. Once lower blood pressure levels are reached and maintained, the slowly increased Methium dosage can usually be stabilized and benefits sustained for prolonged periods.

Prior to treatment each hypertensive should be evaluated individually. Therapeutic response to Methium varies. It is a potent drug and should be used carefully. In the presence of complications such as impaired renal function, coronary artery disease and existing or threatened cerebral vascular accident, caution is particularly indicated. Complete instructions for prescribing Methium are available on request and should be consulted before using the drug.

Methium is supplied in both 125 mg. and 250 mg. scored tablets in bottles of 100 and 500.

1. Grimson, K. S., et al.: J.A.M.A. *149*:215 (May 17) 1952.

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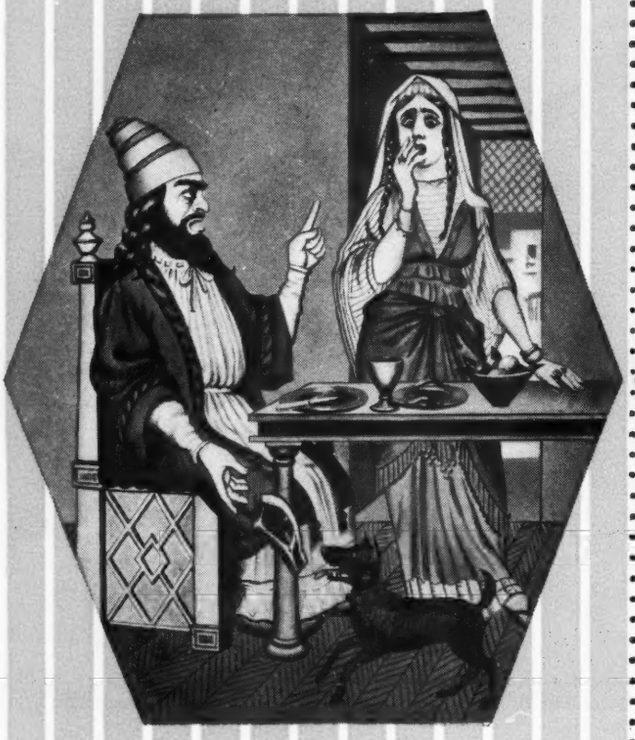

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The American Journal of Medicine

Vol. XIV APRIL, 1953 No. 4

Editorial

Clinical Studies

This paper describes a long-term study of the use of an 80:20 mixture of ammonium and potassium carboxylic resins in the management of congestive heart failure. The authors evaluate critically but fairly the usefulness and limitations of such resins, a subject in which they are unusually well qualified by virtue of experience and detailed observations. They find resins a satisfactory supplement to, and in part replacement of conventional treatment, if proper precautions are taken, but after some six months of regular usage significant electrolyte disturbances are apt to develop. The resins now available do not permit of appreciable liberalization of the sodium intake, as had been hoped.

This is a fairly comprehensive study of the effects of a carboxylic acid cation exchange resin, two-thirds in the acid cycle and one-third in the potassium cycle, on sodium, chloride, potassium, nitrogen and phosphorus balance in eleven patients with difficultly manageable edema due to cardiac or renal disease. Significantly negative sodium balance, with loss of edema fluid, could be achieved even on a low sodium diet. Hyperchloremic acidosis resulted, particularly in patients with intrinsic renal disease. Significant potassium loss was apt to occur but hyponatremia was rarely induced. The authors conclude that if proper precautions, including periodic blood studies, are taken resin therapy is a useful adjunct in the treatment of resistant edema in appropriate cases.

Most investigators have found that cation exchange resins diminish sodium absorption but do not increase excretion of body sodium. In this study of edematous patients on low sodium diets administration of a carboxylic cation exchange resin in sufficient daily dosage caused disappearance of edema and excretion of sodium in amounts greater than dietary intake.

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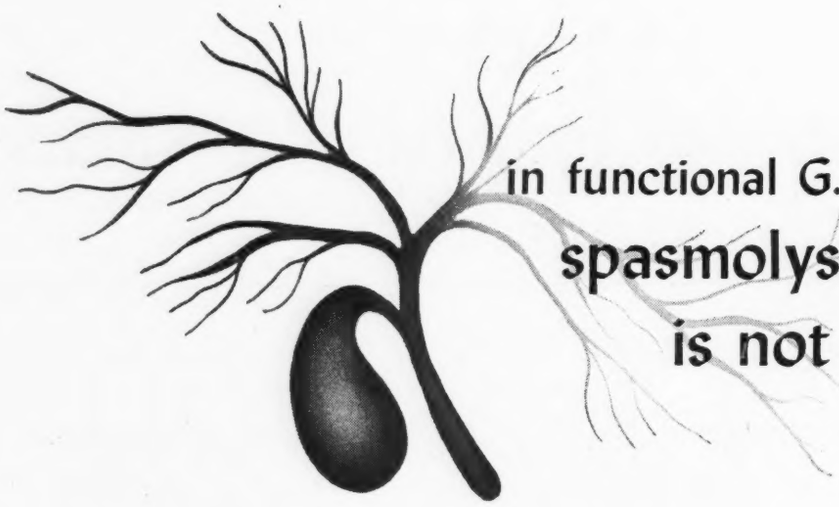

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For prompt and more effective relief of belching, bloating, flatulence, nausea, indigestion and constipation, prescribe *Decholin/Belladonna* for

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- suppresses incoordinate peristalsis
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- increases bile flow and fluidity through *hydro*choleresis
- enhances blood supply to liver
- provides mild, natural laxation – without catharsis

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Dosage: One or, if necessary, two *Decholin/Belladonna* Tablets three times daily.

Composition: Each tablet of *Decholin/Belladonna* contains *Decholin* (dehydrocholic acid, AMES) 3¾ gr., and ext. of belladonna, 1/6 gr. (equivalent to tincture of belladonna, 7 minims). Bottles of 100.

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another feather
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Intrinsic Factor

Organon's long list of achievements has been capped with the development of a reliable intrinsic factor preparation – for the first time guaranteeing oral vitamin B_{12} absorption for *all* patients. Just two tiny Bifacton* tablets (Vitamin B_{12} with Intrinsic Factor Concentrate) constitute 1 U.S.P. anti-anemia unit – sufficient to maintain a pernicious anemia patient for an entire day. Never before have physicians had available a reliable oral anti-anemia preparation of such concentration and potency – never before have they had assured vitamin B_{12} absorption for all patients. Bifacton is available in boxes of 30 tablets.

Organon INC. • ORANGE, N. J.

*Patent Pending

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Conference on Therapy

Clinico-pathologic Conference

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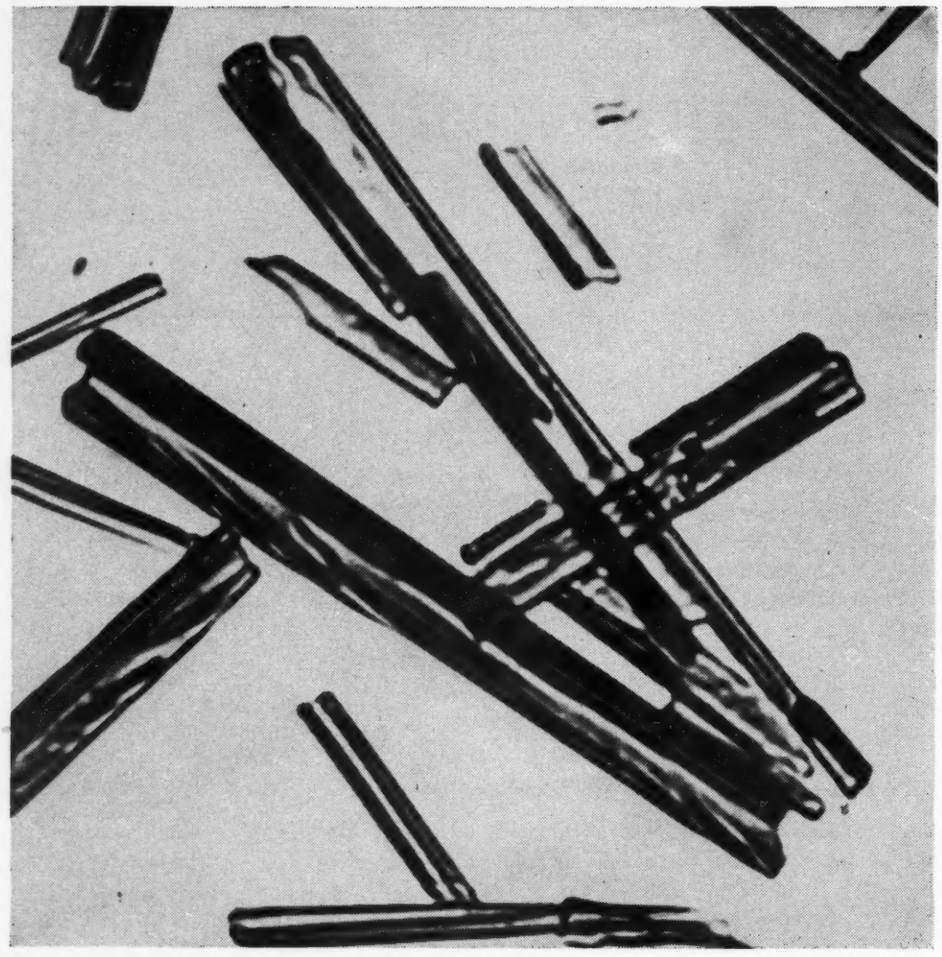

Microphotographs of B_{12} crystals. Their molecules are relatively mammoth in size—the largest of the water-soluble vitamins. And vitamin B_{12} is as exceptional in potency as it is in size.

Mammoth molecule effective in microscopic dosage

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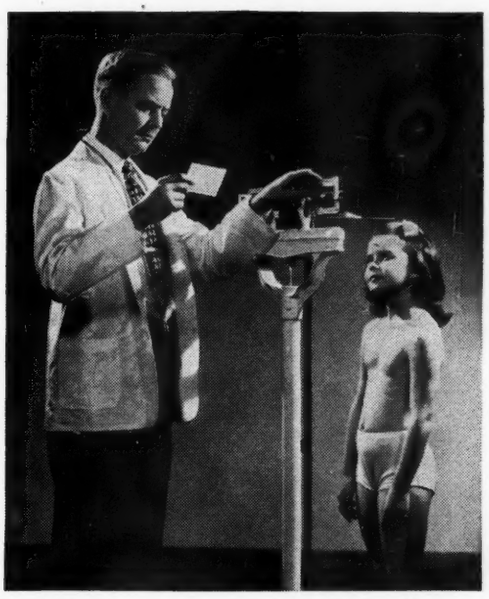

In addition to specific hematopoietic activity, evidence continues to accumulate that in malnutrition, chronic illness and retarded growth in children, vitamin B_{12} supplementation yields ". . . statistically significant enhancement of weight gains . . ."[1]

1. Chow, B.F.: Southern M.J., *45*:604, July, 1952

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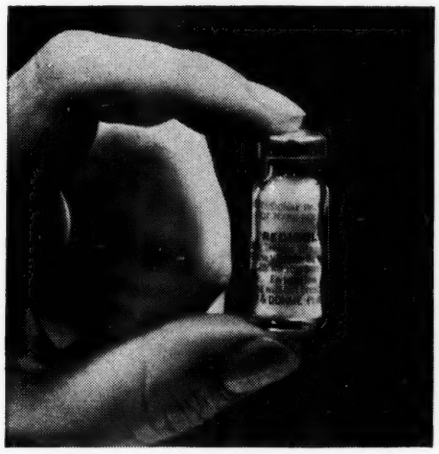

REDISOL, *vitamin B_{12} is available as soluble tablets; 25 mcg. crystalline vitamin B_{12}, vials of 36, bottles of 100; 50 mcg., vials of 36.* REDISOL *Elixir, 5 mcg. per 5 cc., in pint* SPASAVER® *and gallon bottles.* REDISOL *Injectable, 30 mcg. per cc., in 10 cc. vials; 100 mcg. per cc. in 10 cc. vials.*

Vitamin B_{12}—only nutrient therapeutically active in *microgram dose*

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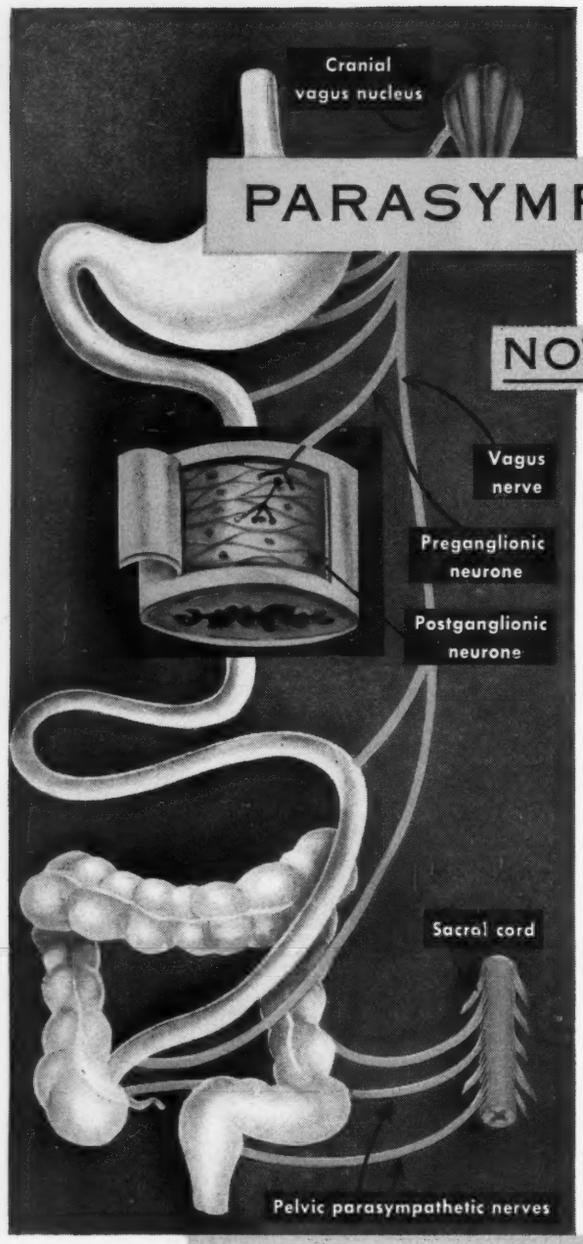

in **GASTROINTESTINAL SPASM**

PARASYMPATHOLYTIC . . .

NOT *parasympathomimetic*

Parasympath*olytic* (as well as spasmolytic) in all therapeutic dosages, homatropine methylbromide affords dependable relief of gastrointestinal spasm. It is thus superior to many agents which are actually parasympath*omimetic* in customary dosages and parasympath*olytic* only in high dosages attended by disturbing side effects.

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For intestinal spasm, biliary spasm, pylorospasm, cardiospasm and irritable colon.

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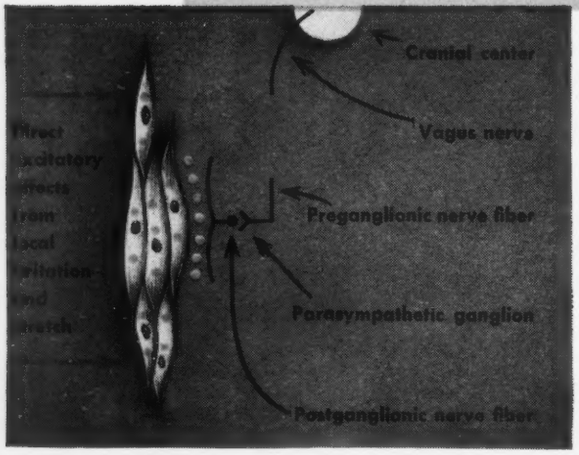
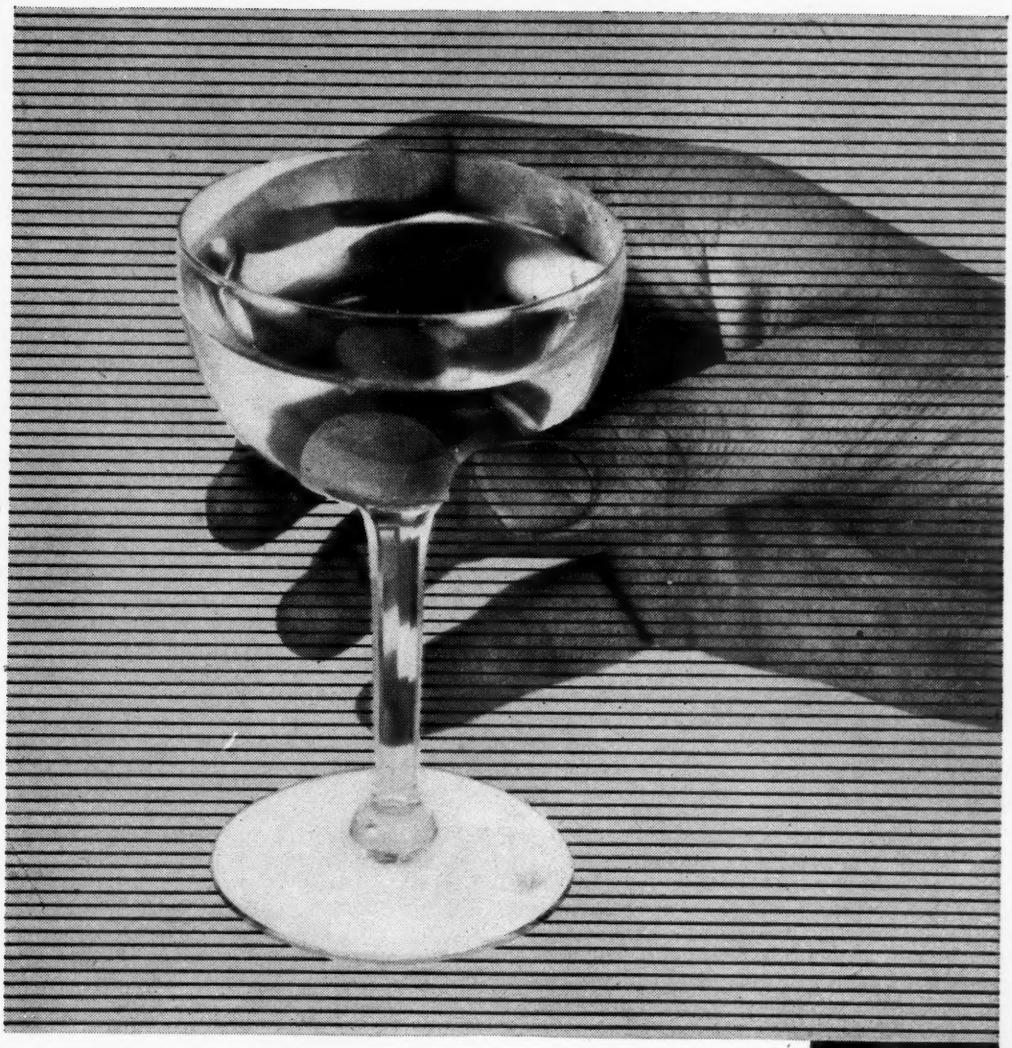


Each tablet contains:

Homatropine methylbromide..5 mg. (1/12 gr.)
(increased from 2.5 mg.)
Alukalin (activated kaolin)....300 mg. (5 gr.)
Phenobarbital .....15 mg. (1/4 gr.)
(increased from 8 mg.)

Supplied: Bottles of 100, 500 and 1000 tablets.



Once the damage is done
High-potency lipotropic therapy is important

When prolonged dietary indiscretion results in liver damage and related disturbances, high-potency lipotropic therapy is indicated. WYCHOL furnishes this.

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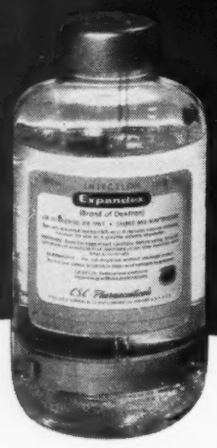
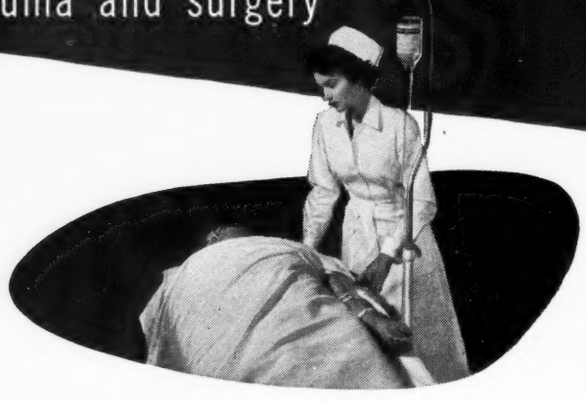
an efficient means of expanding circulating plasma volume

in the treatment of SHOCK due to hemorrhage, burns, trauma and surgery



ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY



Chemistry Expandex (Dextran) Injection, 6% is a sterile, nonpyrogenic 6% (w/v) solution of partially hydrolyzed dextran in isotonic sodium chloride solution. Dextran itself is a water soluble, high molecular weight polymer of glucose, which is produced by the action of the nonpathogenic organism *Leuconostoc mesenteroides* on sucrose. Dextran is closely related to glycogen; both these polysaccharides are made up of glucose units joined by similar linkages.

Pharmacology Given by intravenous infusion, Expandex is an efficient plasma volume expander.[1] As such it produces hemodilution manifested by a decrease in hematocrit and in total protein concentration. A 10% to 15% increase in plasma volume is produced by an infusion of 500 cc. of Expandex, while a 15% to 20% increase is produced by 1,000 cc. In normal individuals, Expandex has no influence on pulse rate, respiration, blood pressure, or ECG. No toxic effect has ever been demonstrated on kidneys, liver, and other vital organs.[2,3,4] Expandex does not interfere with blood typing, crossmatching, or RH determination.

Fate Virtually all injected Expandex can be accounted for through the experimental use of C^{14}-tagged dextran.[5,6,7] From 20% to 40% is excreted in the urine in the first 24 hours; the total urinary excretion of C^{14} activity is 65 to 75%. The bulk of the remaining radioactivity is recoverable in the expired air, indicating metabolism of dextran by the organism. About 2% is found in the feces.

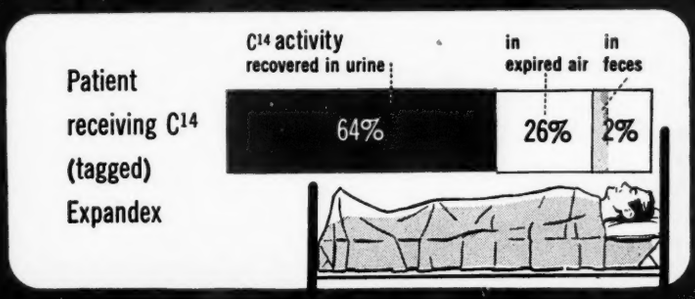
Clinical Results Expandex has been used with excellent results in all types of shock associated with a decrease in effective circulatory volume.[8,9] The plasma volume expansion it produces is maintained for periods sufficiently long to enable the circulatory system to overcome the altered dynamic state. In a typical series,[10] 52 patients in shock were given Expandex. Of these, 44 showed a good response, 5 a temporary response, and only 3 a poor response. Since it is sterile, Expandex does not carry, nor can it transmit, the virus of infectious hepatitis.

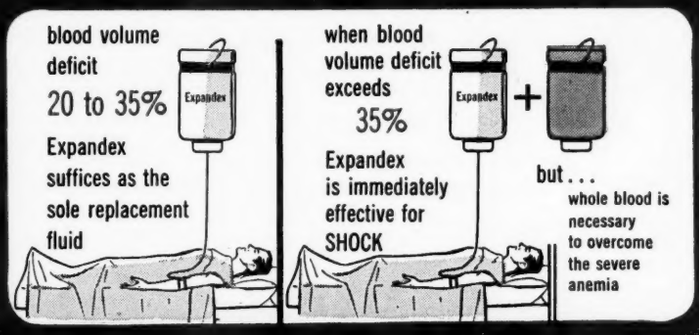
Indications and Dosage

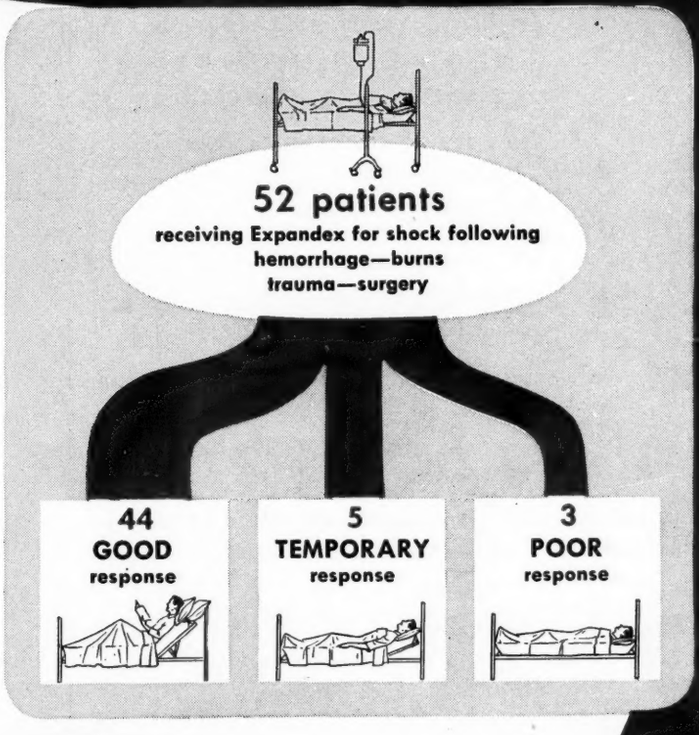
Expandex is indicated in the treatment of shock caused by hemorrhage, burns, trauma and surgery. It can serve as the sole replacement fluid in hemorrhage when the blood deficit does not exceed 35%.[10]

Expandex is given by intravenous infusion; the average dose is 1 or 2 units (500 cc. or 1,000 cc.). A larger quantity safely may be given if required.

These laboratory and clinical findings establish **Expandex** as a safe effective plasma volume expander







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Clinical Advantages of Expandex

1. **It is a clinically effective and notably safe plasma volume expander, indicated in the prevention and treatment of shock due to hemorrhage, burns, trauma and surgery.**
2. **It is slowly metabolized and excreted.**
3. **It does not carry and therefore cannot transmit the virus of hepatitis.**
4. **It does not interfere with the functional activity of any organ or tissue in the body.**
5. **It does not interfere with blood typing procedures or cross-matching.**
6. **It is a nonpyrogenic and sterile solution.**
7. **It is fluid over a wide range of temperatures and is ready for immediate use.**

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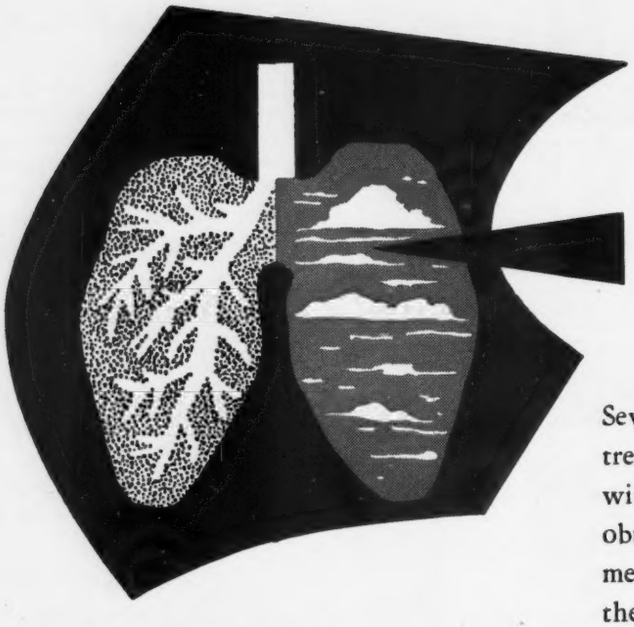
The most significant result in the treatment of *Bronchial Asthma*



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Severe bronchial asthma can now be treated in the home and in the office with a degree of success similar to that obtained with hospital care. Improvement is prompt and dramatic. Neither the patient's age nor the chronicity of the asthmatic condition detracts from the efficacy of ACTHAR treatment, which has stood the most severe of all tests of usefulness—the requirements of the general practitioner. The use of the disposable cartridge syringe—an immediately available form of HP* ACTHAR *Gel*—can be a life-saving measure in the medical emergency which suddenly arises in the course of long-standing "intractable" asthma. HP*ACTHAR *Gel* has demonstrated its superiority over customary measures in many instances of bronchial asthma, and has brought about gratifying remissions lasting as long as 18 months.

Advantages

Administered as Easily as Insulin:
Subcutaneously or intramuscularly with a minimum of discomfort.

Fewer Injections:
One or two doses per week in many instances.

Rapid Response, Prolonged Effect:
Combines the two-fold advantage of sustained action over prolonged periods of time with the quick response of lyophilized ACTHAR.

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FOR

Continuous Acid Neutralization

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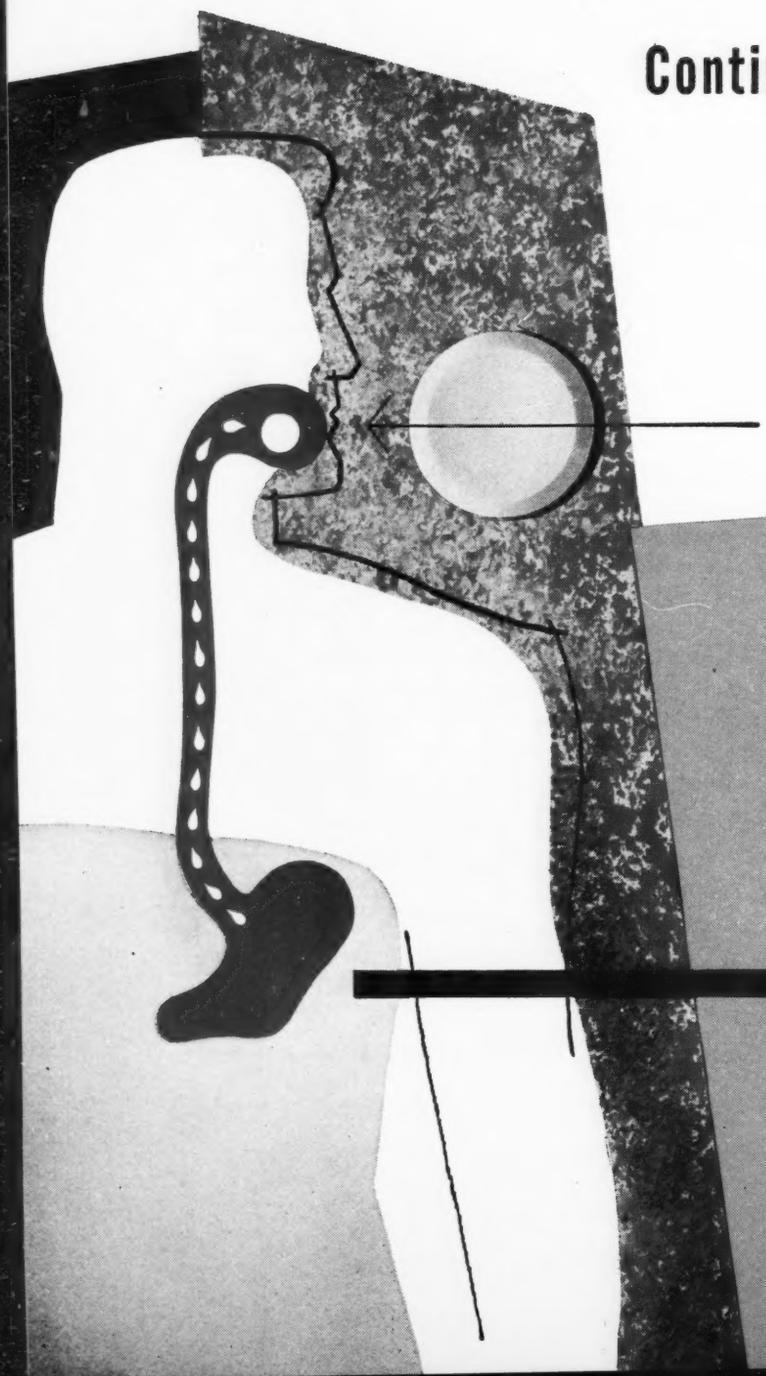

Comparable to Drip Therapy

but free from its inconvenience

and its difficulties

1. Douthwaite, A. H., and Shaw, A. B.: The Control of Gastric Acidity, Brit. M. J. 2:180 (July 26) 1952.

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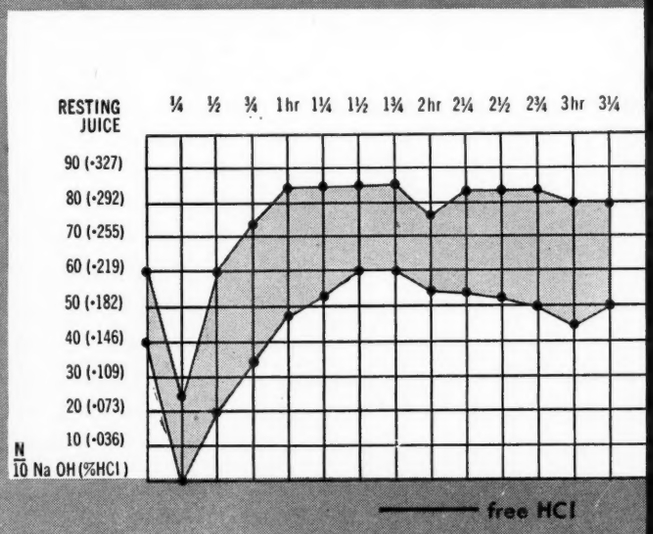
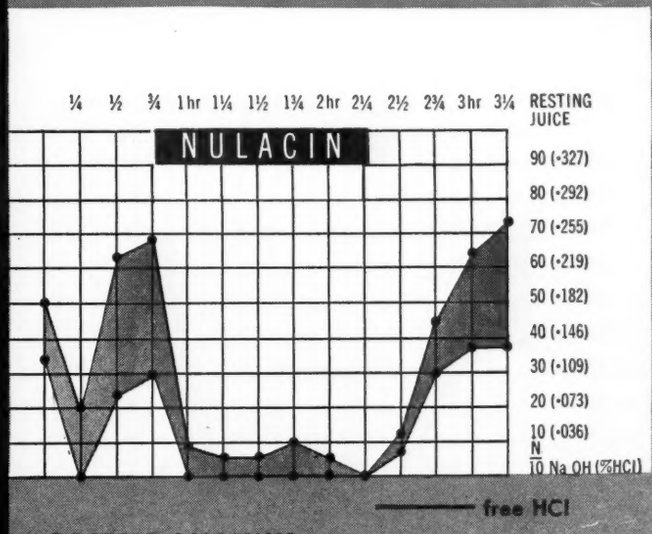


GASTRIC ANALYSIS. Superimposed gruel fractional test-meal curves of five patients with peptic ulcer.



GASTRIC ANALYSIS. Same patients, two days later showing the profound and sustained neutralizing effect of sucking Nulacin tablets (three an hour).

Continuous neutralization of the gastric contents, the *sine qua non* of successful peptic ulcer therapy, is conveniently and effectively achieved with Nulacin tablets.

Placed between the gum of the upper jaw and the cheek, and allowed to dissolve, the Nulacin tablet slowly releases its acid-combining ingredients. Thus its maintained antacid effect is comparable to that of continuous intragastric drip, but is free from the disadvantages and inconveniences of the latter.[1]

Highly palatable and providing only 11 calories, each Nulacin tablet is prepared from milk combined with dextrins and maltose and incorporates:

Magnesium trisilicate	3.5 gr.
Magnesium oxide	2.0 gr.
Calcium carbonate	2.0 gr.
Magnesium carbonate	0.5 gr.
Ol. menth. pip.	q.s.

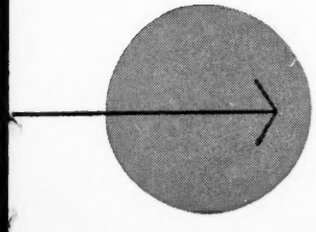
The efficacy of these antacids is enhanced manyfold by the unique method of administration employed in the form of Nulacin.[2]

The Nulacin tablet is lozenge-shaped for convenient retention in the buccal sulcus, and of proper hardness to avoid too rapid disintegration.

For the treatment of active ulcer, the patient should be instructed to suck Nulacin tablets, two or three every hour, beginning one-half to one hour after each meal.

During quiescent periods, the suggested dose is two tablets between meals, beginning half an hour after each meal. The efficacy of the tablet is greatly reduced if it is chewed and swallowed.

Nulacin is available in distinctive prescription-label tubes of 25 tablets at all pharmacies.



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- High, sustained blood levels

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therapy

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GYNETONE,* a new convenient combination of 1 mg. Estradiol U.S.P. and 10 mg Methyltestosterone U.S.P. in tablet form, provides prompt, uncomplicated relief from menopausal symptoms.

Synergistic and additive actions, as well as virtual elimination of the occasional side effects attending the use of either hormone alone, are assured by GYNETONE.

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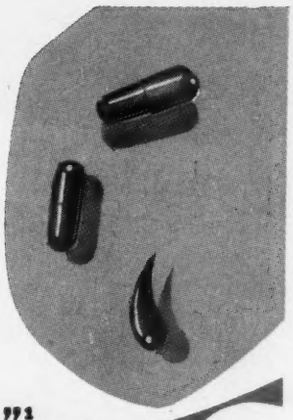

"where the liver is damaged

administration of

LIPOTROPICS

is indicated"[1]

IN GERIATRIC PATIENTS

"There is no doubt that many persons, especially those of advanced age, have functional and structural hepatic alterations. Many times the hepatic deficiency is but slightly apparent or nonapparent...."[1]

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"The present study indicates the uniform presence of liver damage in human obesity as manifested by liver function tests and biopsies."[2]

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1. Pollak, O. J.: Delaware State M. J. *24*:157, 1952.
2. Zelman, S.: Arch. Int. Med. *90*:141, 1952.

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---

*Food for Your Heart, a Manual for Patient and Physician, Department of Nutrition, Harvard School of Public Health, Harvard University, The American Heart Association, Inc., New York, 1952. Copies available through local Heart Association.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

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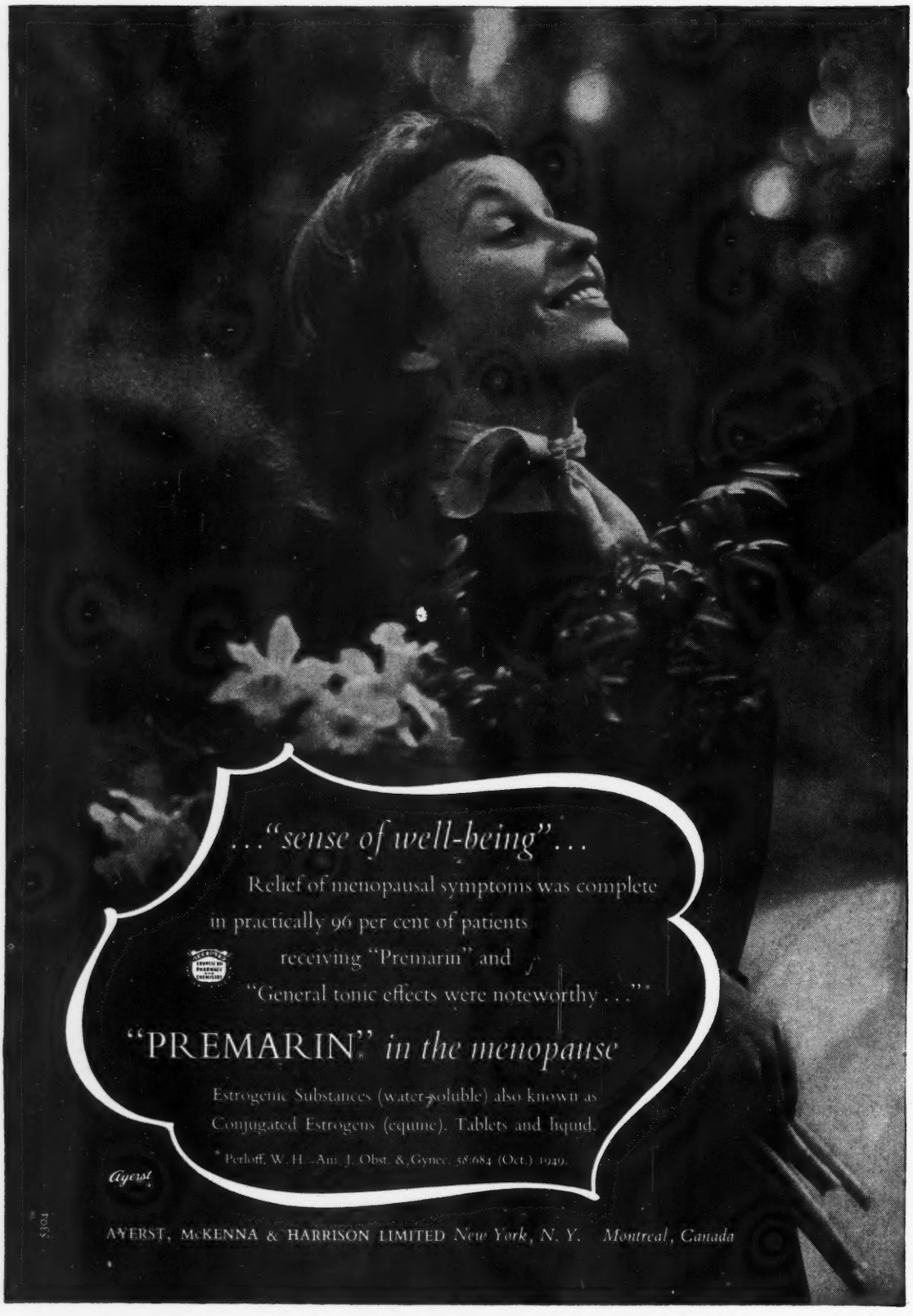
Main Office, Chicago...Members Throughout the United States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* Perloff, W. H.—Am. J. Obst. & Gynec. 58:684 (Oct.) 1949.
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Anatomy *of the* Neck

1. Parotid gland
2. Superficial temporal artery & vein
3. Temporal branch of facial nerve
4. External carotid artery & posterior facial vein
5. Superficial cervical lymph nodes
6. External jugular vein
7. Accessory nerve & internal carotid artery
8. Platysma muscle
9. Fourth cervical nerve
10. Superior position of sternocleidomastoid muscle
11. Deep cervical lymph nodes
12. Fifth cervical nerve
13. Posterior supraclavicular nerve & anterior jugular vein
14. Superficial cervical artery & vein
15. Middle supraclavicular nerve & subclavian artery
16. Transverse scapular artery & vein
17. Inferior position of sternocleidomastoid muscle
18. External maxillary artery & anterior facial vein
19. Submaxillary lymph nodes & digastric muscle
20. Submaxillary gland & mylohyoid muscle
21. Submental lymph nodes & hypoglossal nerve
22. Superior laryngeal artery & nerve
23. Superior cervical ganglion
24. Superior laryngeal vein & omohyoid muscle
25. Superior thyroid artery & vein
26. Ansa hypoglossi
27. Common carotid artery & sternothyroid muscle
28. Middle cervical ganglion & phrenic nerve
29. Vagus nerve
30. Thyroid gland & middle thyroid vein
31. Internal jugular vein
32. Sternohyoid muscle
33. Jugular lymphatic trunk
34. Inferior thyroid veins

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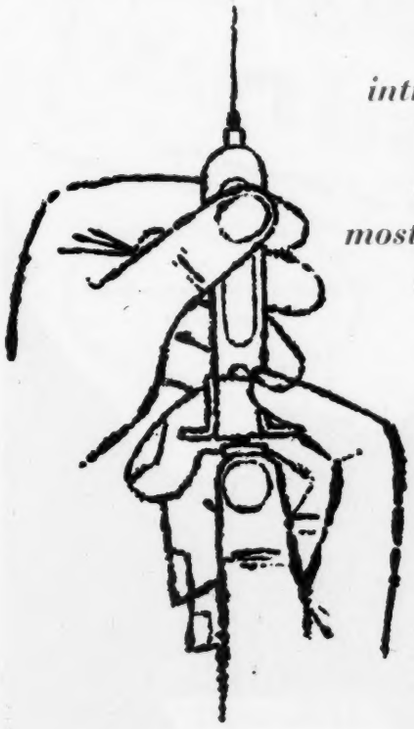

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The American Journal of Medicine

Vol. XIV APRIL, 1953 No. 4

Editorial

The Future of Electrocardiography

With the recent death of Doctor Frank Norman Wilson, Professor of Medicine at the University of Michigan, an unusually productive era in the field of electrocardiography has come to a close. Wilson was universally acknowledged as the leader in his field. On the sad occasion of his death a brief review of his fundamental contributions, which lifted a relatively empiric modality to a precise, scientific level, may make it possible to predict what the clinician and the investigator can expect in the way of advances in the future.

On superficial examination it would not seem that any further progress can be made in electrocardiography. True, vectorcardiography has enjoyed a renascence, and the spatial vector method of synthesis of surface leads has proven useful in diagnosis and teaching. But the latter is merely a way of visualizing, and the former a method of presenting the same electrical information provided by conventional leads. Neither is likely to add much of value diagnostically, although both have added a great deal to our understanding of the genesis of the deflections seen in the leads usually recorded in the clinic.

When remarking that no further progress seems possible, one is reminded of a similar statement often heard in the late twenties. There was a general conviction then that electrocardiography was a rather barren field for a young investigator to enter. It was pointed out that Einthoven had elaborated most of the physical principles, and Rothberger and Lewis had already done practically all that could be done experimentally and clinically on the arrhythmias. Indeed, the latter as early as 1912 spoke of the imminent end of the "new chapter of clinical medicine" concerned with "deciphering" irregularities of the ventricles and "disorder in the sequence of contraction in (the heart's) chambers." At the same time, however, Lewis did prophesy that much information might be given by an electrocardiogram even when the rhythm was regular. He had in mind modifications of the ventricular and possibly the atrial deflections caused by disease of these chambers. This phase of the method had received scant attention up to that time. He himself made some research endeavors along this line but they were not as productive as were his investigations of the rhythms. Possibly for this reason he completely abandoned all further investigation in the field in 1924 in order to devote his time to clinical research on the peripheral circulation. This act on the part of the master undoubtedly convinced many that electrocardiography had reached a permanently sterile end.

The history of scientific endeavor has repeatedly shown the hazard of predicting that progress in any field of investigation is no longer possible. The belief that the end of productivity in electrocardiography came in 1924 has since been proven to be the grossest sort of error. Those most responsible for reversing the miscalculation were Wilson and his associates.

Wilson's interest in electrocardiography began in 1913 but the contribution which first called attention to him was the one appearing in 1932 in which he analyzed direct leads made from the human heart three years earlier by his associates, Barker and Macleod. In this analysis he demonstrated that the previous nomenclature for bundle-branch block was in error. A half a dozen years before that he wrote about the laws governing currents in volume conductors, but it was the monograph on currents of action and of injury with Macleod and Barker published also in 1932 which focused attention on the significance of the conducting medium in determining the form of the electrogram obtained from excitable tissues. It left no doubt about the fundamental error in the negativity hypothesis which had dominated physiologic thought up to that time and substituted for it the bipolar hypothesis which is still generally accepted.

Because these basic researches were quite

profound they received little attention. Yet they were the very foundation of the subsequent experimental and clinical work which Wilson did on the interpretation of direct and precordial leads in myocardial infarction which have been so useful clinically. Further, the significance of the areas of electrocardiographic deflections, the concept of the ventricular gradient, and the development of the indifferent central terminal were all advances of the greatest clinical usefulness which stemmed from Wilson's application of basic physical laws to the solution of the electrocardiographic problems of the clinician.

In retrospect, progress in the field of electrocardiography has been very considerable over the last two and a half decades despite earlier predictions to the contrary. Not all of this advance came out of the laboratory at Ann Arbor but the potent stimulus for it unequivocally did. The situation in 1952, occasioned by Wilson's passing, is in some respects comparable to the situation in 1924, when Lewis retired from the field. And the question again confronts Medicine: What further progress can be made in electrocardiography?

This time the prediction must be more cautious. The reasons are fairly obvious. The embarrassing error of the past must not be repeated. Further, the world has changed, science is in the ascendancy; and when capable young minds are turned loose on any kind of problem in this quantitative era of vastly improved instrumentation and accelerated research, the field of endeavor, no matter what it might be, can hardly be expected to remain static.

As of this writing, it would seem that progress is most likely to be made by an intensive study of the source of the electromotive force itself, namely, the myocardial cell. This is, to be sure, research of a fundamental nature of immediate concern to the clinician only as it may lead to clinically useful methods. Further, the clinician will be interested, just as he is today, not so much in the bioelectric behavior of the cell as he will in how that behavior reflects the primary function of the myocardial cell to contract. It is more than likely that precise quantitative relationships exist between the electrical events, on the one hand, and the mechanical and chemical processes in the cell on the other. The latter include the interaction of actin and myosin, the augmenting effect on this union of adenosine triphosphate, the repelling effect of potassium and the changes in the ionic permeability of the cellular membrane. That these processes bear some sort of measurable relationship to depolarization and repolarization of the cellular membrane will almost certainly be demonstrated in time. And when they are demonstrated, the clinician will be in a position to measure them because even now he has available methods of quantitating the membranous ionic or electronic processes of depolarization and repolarization both in atrial and ventricular muscle.

The desirability of knowing more about, and having finer measurements of, the energetics of the myocardial cell seems obvious enough. It must be admitted that little is known about why the heart fails, and it is at times even difficult to say from a clinical examination whether it is failing or not. The methods to be used to gather this information are somewhat less certain but it need hardly be pointed out that the electrocardiogram in any form provides two variables, voltage and time, from which at least the electrical energetics of the myocardial cell may be estimated. This calculation has been made in this laboratory from the time corrected spatial vectorcardiogram of man. The electrical energy involved is expressed as a ratio, the D/R (depolarization-repolarization) ratio, or as a sum, CEC (cyclical energy consumption).

If the electrical energetics can be estimated clinically, and if fixed or known variable quantitative relations exist between these and the chemical and mechanical functions of the cell, it should be possible to estimate the latter from a measurement of the former. The clinical value of such quantities remains to be determined but it seems likely that it will be considerable.

Will further progress of a clinically useful kind be made in electrocardiography? The portents as they now exist make it inevitable. However, the form this progress will take may bear little resemblance to clinical electrocardiography as practiced today.

CHARLES E. KOSSMANN, M.D.
New York University College of Medicine, New York, N. Y.

Clinical Studies

Biochemical Disturbances and Clinical Symptoms during Prolonged Exchange Resin Therapy in Congestive Heart Failure*

LAWRENCE GREENMAN, M.D., J. B. SHALER, M.D. *and* T. S. DANOWSKI, M.D.
Pittsburgh, Pennsylvania

CERTAIN forms of cation exchange resins prevent, minimize or deliver generalized edema by removing small amounts of sodium from the intestinal tract and by acting as acidifying diuretics.[1–5] In the exchange process, however, potassium is usually bound in greater amounts than sodium, and calcium, magnesium and other substances which act as cations when in solution may also be removed.[1,6–9] The safety with which these effects can be elicited for relatively short intervals has been demonstrated by careful balance data.[1,2,4,11,12] The place of these agents in long-term treatment of edema has not been defined despite the numerous publications concerning their usefulness.[13–26] We have therefore administered carboxylic cation exchange resins to twelve patients with congestive heart failure for intervals up to fifteen months in length. The results indicate that resins are efficacious and relatively safe supplements to the treatment of this type of edema for a limited number of months, and that periodic observations are necessary to detect and correct the significant biochemical alterations which may supervene before clinical abnormalities are observed.

TABLE I

DIAGNOSES, AGE, SEX AND THERAPY OF PATIENTS PRIOR TO RESIN ADMINISTRATION

Patient, Age and Sex	Diagnoses						Treatment			
	Etiology	Enlargement	Valvular Damage (MS)	(MI)	(AI)	Rhythm	Congestive Failure (grade)	Diet Na (gm./day)	Digitalis (gm./day)	NH_4Cl (gm./wk.)	Hg Diuretic (times/mo.)
C. M., 47, F	RHD	+	+	+	+	AF	IV D	0.3	0.1	24	2–4
F. R., 43, F	RHD	+	+	+	+	AF	III D	0.5	0.05*	24	4
F. Vr., 26, F	RHD	+	+	+	+	AF	IV E	0.3	0.1	24	4
D. R., 23, F	RHD	+	+			NSR	III D	0.5	0	24	4
G. S., 37, F	RHD	+	+			NSR	III D	0.5	0.1	24	2–4
R. L., 59, M	RHD	+	+			AF	III D; ang.	†	0	0	0
H. M., 45, M	HCVD	+	None			NSR	IV E	0.3	0	24	‡
S. H., 52, F	HCVD	+	None			NSR	III D	†	0.1	24	1–2
F. V., 71, M	Art; HCVD	+	None			NSR	III D; ang.	†	0.1	24	0
M. F., 41, F	HCVD	+	None			AF	IV E	0.3	0.1	15	4
J. R., 68, F	Art; CVD		None			AF	IV D	†	0.1	24	0
A. C., 62, F	Art; CVD	+	None			NSR	IV D	0.3	0.1	24	4

RHD = Rheumatic heart disease
Art. = Arteriosclerosis
HCVD = Hypertensive cardiovascular disease
CVD = Cardiovascular disease
MS = Mitral stenosis
MI = Mitral insufficiency
AI = Aortic insufficiency
AF = Auricular fibrillation
NSR = Normal sinus rhythm
Ang. = Angina
* Digitoxin (mg.)
† Regular diet without salt shaker
‡ Given at one- to two-day intervals five times during the seven days preceding resin therapy

* From the Department of Research Medicine, the Children's Hospital of Pittsburgh, the Presbyterian and Woman's Hospital, the Falk Clinic of the University of Pittsburgh School of Medicine, Pittsburgh, Pa.

PATIENTS AND METHOD OF STUDY

Twelve adults, three males and nine females varying in age from twenty-three to seventy-one years, were treated with exchange resins. The patients, all of whom had severe congestive heart failure and edema, were selected from the Falk Cardiac Clinic and the private practice of one of us (J. S.). Patients with definite renal disease were excluded. All but three had been hospitalized in the past for treatment of heart failure. The diagnoses, age, sex and therapy of the patients at the start of resin administration are listed in Table I. In each instance the former regimen of treatment was continued without change in the degree of sodium restriction but with elimination of ammonium chloride and the mercurial diuretics. A carboxylic cation exchange resin, 80 per cent in the hydrogen and 20 per cent in the potassium form, was then administered immediately after meals and at bedtime in four doses totalling 45 gm. or more daily.

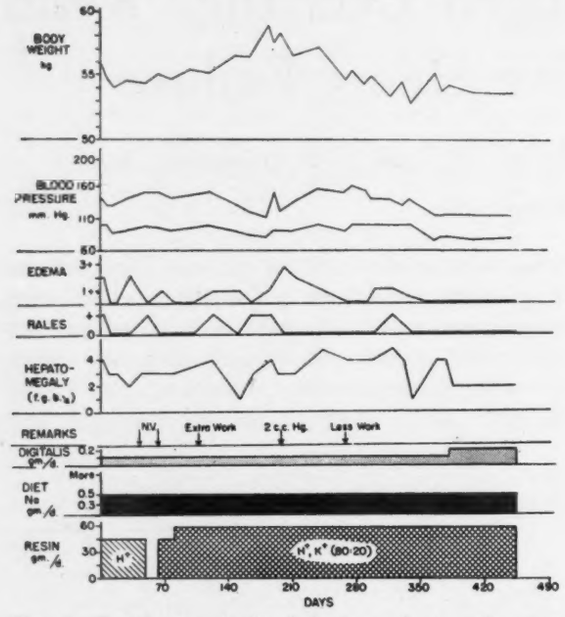

FIG. 1. C. M., hospitalized 5 times during the past 4 years because of congestive heart failure; complained of gastric distress during the first three days of resin therapy. On the 42nd day the patient developed nausea and vomiting and discontinued the resin from the 48th to the 60th day. On the 63rd day she was started on the mixture of hydrogen and potassium forms which she took in the same amount for the next 7 weeks without complaint. At the end of this time 1 plus ankle edema, dyspnea on slight exertion and hepatomegaly were still present. The resin was therefore increased to 60 gm. per day. On the 182nd day increased congestive failure with cough, few rales at both lung bases, ankle edema and both hepatic and splenic enlargement appeared. These developments followed upon an increased burden of housework. Since the symptoms increased and the edema became 3 plus, she was given 2 cc. of a mercurial diuretic intravenously on the 196th day with an adequate diuresis. She has not required further injections since her activities have decreased. When last seen in July, 1952, she had no cough, no edema, lungs were clear, liver and spleen were palpable and she was fairly comfortable.

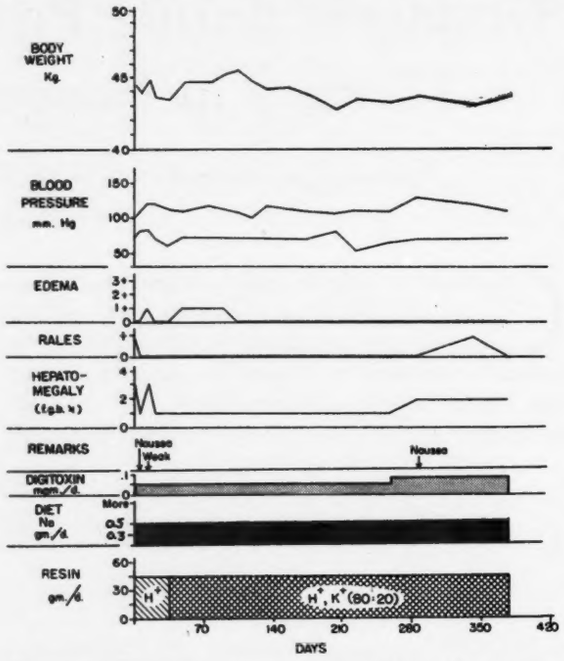

FIG. 2. F. R. reported nausea, weakness, listlessness, constipation and bloating after the resin was started. In several days the nausea had disappeared and her only complaints were constipation and bloating. She received the H^+ form of the resin for 35 days and then was placed on the combination of H^+ and K^+ forms. She prefers to take the resin for 6 days a week since she believes this prevents many of her gastrointestinal complaints. On the 259th day the digitoxin was increased to 0.2 mg. every other day; and on her last visit to clinic on June 27, 1952, she had no intestinal difficulties.

All of the subjects of this study were followed as outpatients at one- to two-week periods for the first month of therapy and at monthly intervals thereafter unless there was a pertinent reason for an earlier visit. Each time they were questioned about their subjective response to the resin, as well as the presence of edema, dyspnea, cough, gastrointestinal and urinary symptoms. Blood pressure and pulse were recorded and the heart, lungs, abdomen and extremities examined. Cardiac function was graded in accordance with the criteria of the New York Heart Association.[27] The protocols are appended, together with figures describing

the clinical response of the patients. (Figs. 1 to 6.)

Before starting therapy blood was withdrawn for non-protein nitrogen analysis as well as for determination of serum bicarbonate, chloride, sodium, potassium, total protein, albumin, globulin, calcium and phosphorus levels. In addition, all but one patient had a urinalysis within the first week of treatment. The chemical methods employed were those in regular use in this laboratory.[1] These blood studies were usually repeated at frequent intervals during the first month and then at one- to two-month periods unless otherwise indicated. Urinalyses were infrequently repeated.

RESULTS

Effects on Edema. Edema was adequately controlled without the supplementary use of additional diuretics in all patients but two, even when resin therapy was continued as long as fifteen months. Five of the subjects became edema-free within one week; two within two weeks; and two others in four weeks. The edema

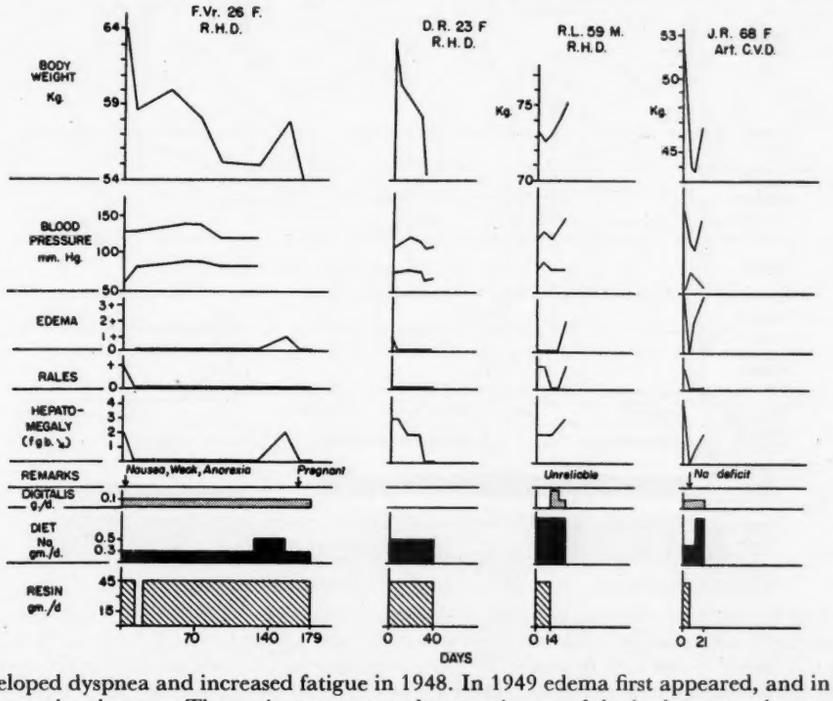

FIG. 3. F. Vr. developed dyspnea and increased fatigue in 1948. In 1949 edema first appeared, and in the past year she has had palpitation and orthopnea. The patient was started on a mixture of the hydrogen and potassium forms of the resin, 45 gm. per day, while hospitalized for congestive failure. During the first week she complained of nausea and weakness and the resin was discontinued for one week. She has succeeded in ingesting the exchanger regularly since then, despite periodic complaints of abdominal distress, gas and slight nausea. Dietary sodium was increased to 500 mg. per day on the 155th day; however, she developed edema and hepatomegaly. On her last visit in August, 1952, she was feeling fairly well, had no edema but was eating poorly. She was 10 weeks pregnant at this time.

D. R. was started on the mixture of H^+ and K^+ forms of the resin on November 1, 1951. She noted an increase to 3 a day in the number of her bowel movements but did not have diarrhea or other difficulty. The exchanger was discontinued on the 40th day when she underwent a mitral valvulotomy. She has not required any medication since then.

R. L. was started on 45 gm. per day of a mixture of hydrogen and potassium forms of the cation exchange resin on June 8, 1951. His past history included gonorrhea and primary syphilis in 1913 for which he was adequately treated. His serologic test for syphilis is negative. He had worked for 14 years in a foundry and was forced to retire because of the dust. During the past 5 years he had noted dyspnea on exertion, and had stopped work at the post office 3 years ago because of dyspnea. For 7 months he had been troubled with increasing weakness, nervousness, orthopnea, nocturnal paroxysmal dyspnea, cough at night productive of heavy white sputum without blood, and substernal pain on effort relieved by rest. No edema had been noted. He was placed on resin as well as a diet without added salt since he refused to accept one more stringently limited. He did not receive digitalis. Within 2 weeks his rales had disappeared but there was no change in his symptoms. He was uncooperative, ingested the resin irregularly and complained of its taste and gastric irritation. The exchanger was discontinued on the 14th day and he was placed on digitalis.

J. R. was started on the H^+, K^+ forms of the exchanger on May 16, 1952. She complained of anorexia, fatigue, generalized aching, dyspnea, orthopnea and edema for 3 months beforehand. She developed gastric distress, nausea and vomiting and both sodium and potassium depletion during the week she ingested the resin. (See *Results* for further details.)

was reduced to a minimum in nine days in one patient but did not disappear completely until two months had elapsed. One patient has not been completely free of edema despite 371 days of treatment but this may be a manifestation of extensive varices since he has improved clinically. The twelfth patient had no peripheral edema at the start of therapy but rales which had been present at both bases disappeared within two weeks. Changes in body weight and liver size usually reflected these changes in body fluid. In contrast to the frequent hospital admissions previously necessary for treatment of congestive failure, only one patient, R. L., subsequently required hospitalization. He was, however, the least reliable of the group in taking digitalis and resin, and in restricting sodium intake.

We were not successful, however, in permitting a more liberal sodium intake in these patients. In four subjects (F. Vr., S. H., M. F., A. C.) dietary sodium was moderately increased with immediate gain in body weight and development of edema and hepatomegaly. The first three returned to their previous condition when the sodium was reduced. The fourth (A. C.) refused to limit her intake of sodium again; she is the one person in this series who still requires repeated mercurial injections despite resin therapy. The exact changes in sodium intake unsuccessfully attempted by these subjects were the following: F. Vr. from 0.3 gm. per day to 0.5; M. C. and A. C. from 0.3 gm. to a diet without a salt shaker; and S. H. from a diet which omitted extra salt to one utilizing small amounts.

Four patients (G. S., H. M., S. H., J. R.) who had been edema-free on resin therapy became edematous, gained weight and developed hepatic enlargement within a few days following

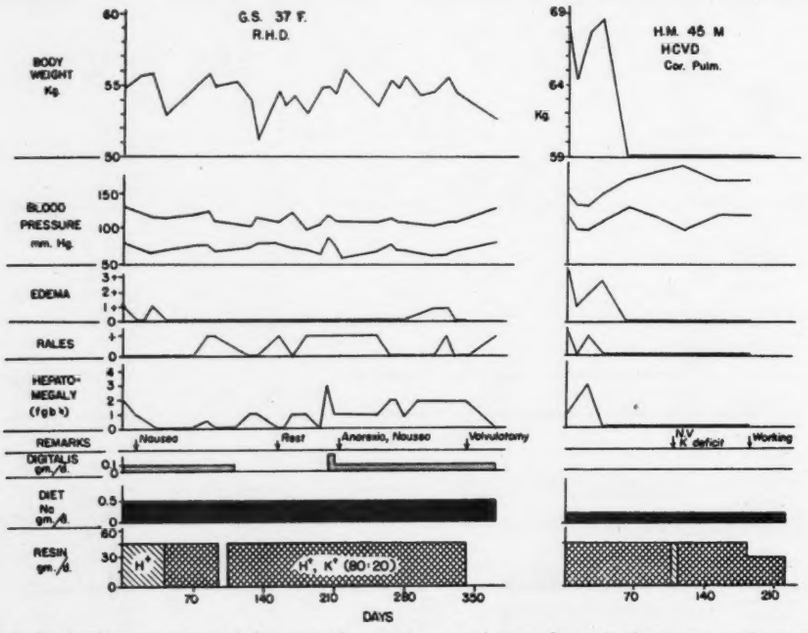

FIG. 4. G. S. received the hydrogen form of the resin for 42 days and complained of nausea and gastrointestinal distress during the first two days. The resin was discontinued when she was hospitalized for removal of a lipoma; edema recurred within one day and subsided with re-institution of resin treatment. On the 42nd day the H^+ form was replaced by a mixture of H^+ and K^+ forms in the same dosage. The patient remained on this therapy for a total of 340 days when it was discontinued because she underwent a mitral valvulotomy on May 27, 1952. Since surgery she has been greatly improved and been maintained on digitalis and relative sodium restriction.

H. M. was started on the H^+, K^+ forms of the cation exchanger on January 5, 1952 while hospitalized for congestive failure. The resin was changed to the hydrogen form alone in the same dosage on the 97th day, because our supplies of the former exchanger were temporarily exhausted. The patient developed gastric irritation, nausea, vomiting, anorexia and potassium depletion. (See *Results* for details.) His electrocardiogram (Fig. 7A) was distinctly abnormal with many ventricular premature beats but no specific signs of potassium intoxication. He had not been receiving digitalis. The resin was temporarily discontinued and he received supplementary KCl with dramatic relief. His electrocardiogram (Fig. 7B) became regular but was still abnormal. He was then re-started on the hydrogen, potassium resin which he has taken without distress. He has been feeling and eating well and has started to work. On the 173rd day he reduced the resin to 30 gm. per day without ill effects.

discontinuation of the exchanger. All but J. R. were restarted on treatment with disappearance of these findings. Two patients (C. M., F. V.) required 60 gm. of the resin per day. C. M. also needed a single injection of a mercurial diuretic. The resin for F. V. was increased on however, also complained of weakness while on the resin.

Gastrointestinal Effects. During the first two to three weeks of treatment all patients objected to the grittiness and bulk of the resin. The majority preferred to mix the resin with water

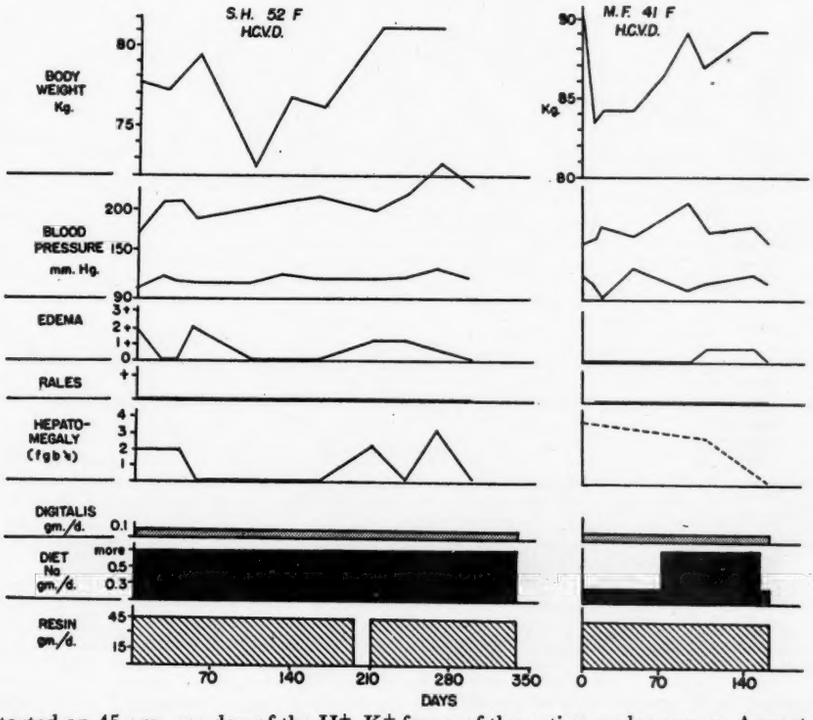

FIG. 5. S. H. was started on 45 gm. per day of the H^+, K^+ forms of the cation exchanger on August 27, 1951. Sodium restriction was irregular and consisted of partial elimination of the salt shaker. She developed temporary gastric distress for 2 days after starting treatment and complained of constipation, but preferred the present therapy to the injections. She discontinued the resin on the 147th day because she had used up her supplies. When she was seen two weeks later, she had recurrence of her edema and hepatomegaly. These findings disappeared promptly when resin was re-started. She has been on treatment for 335 days at present. Her complaints have included paroxysmal dizziness and occasional blacking out. These events had occurred before resin was instituted however.

M. F. was started on the H^+, K^+ forms of the resin on November 2, 1951, while hospitalized for congestive failure. Prior therapy had included ammonium chloride 3.0 gm. per day 5 days a week and a mercurial diuretic 1 to 3 times a week for at least 4 years. Her diet had been limited to 300 mg. of sodium per day. In 1946 the patient had a bilateral lumbodorsal sympathectomy because of hypertension and headaches. The headaches disappeared although the hypertension persisted. The patient tolerated therapy well with gradual increase in strength, control of edema and disappearance of hepatomegaly. The 3 plus albuminuria and granular casts present at the start of resin therapy disappeared.

the 351st day when his heart failure unaccountably became worse.

All the patients who had been receiving mercurials previously said they preferred resin therapy to mercurial diuresis. The latter frequently left them feeling weak and tired. In addition they objected to the reaccumulation of fluid which occurred before the next injection. They preferred the relatively even control of edema achieved by resin ingestion. Five of the patients (F. Vr., H. M., F. V., J. R., A. C.), and drink the suspension as rapidly as possible. The remainder used cold grapefruit juice or carbonated beverages. Initially, all of them reported gastric irritation and eructation immediately after its ingestion. These complaints subsequently subsided. Seven subjects had nausea and three of them vomited occasionally; three complained of anorexia; six were constipated; and one had an increase in frequency of formed stool to three per day; two complained of bloating; and one of increased thirst. F. R. preferred to take the

resin only six days a week because gastric distress and constipation developed when taking it continuously. Control of her edema has been satisfactory with this schedule.

Even when therapy was continued for fifteen months, no obvious evidences of vitamin deficiences were observed.

only one blood analysis during resin therapy. The increase in chloride was not always equal in magnitude to the decrease in bicarbonate.

In five patients (C. M., F. R., F. Vr., G. S., J. R.) hyponatremia developed during therapy, with sodium concentrations of 134 mEq. or less. All were eating poorly at the time. In C. M.

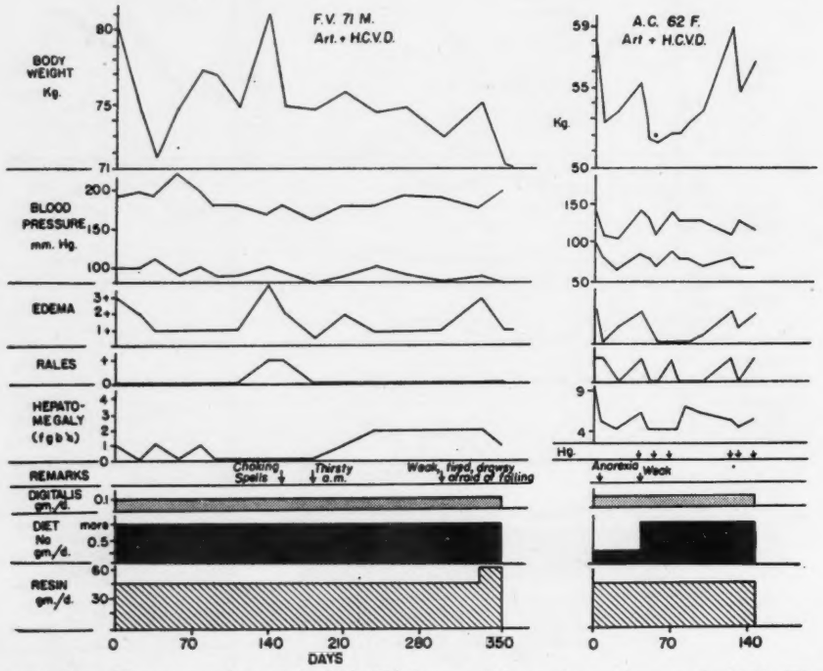

FIG. 6. F. V. was started on 45 gm. per day of the H^+, K^+ forms of the resin on August 3, 1951. The patient refused a low sodium diet but did reduce the use of the salt shaker. The resin produced slight gastric distress temporarily. On the 135th day the patient temporarily reduced his resin intake by half. On the 335th day his edema had again increased so the resin was raised to 60 gm. per day. This was followed by a large diuresis with delivery of almost all the extra fluid, increased weakness, difficulty in walking and drowsiness. The serum potassium was abnormally low at this time and he was given supplementary potassium citrate, 6.0 gm. per day for 5 days without clinical change, but with elevation of his serum potassium to 3.6 mEq./L.

A. C. was started on the H^+, K^+ forms of the exchanger on January 22, 1952. Three years before she had a myocardial infarction. Edema had been present for the past 2 years and ascites for 8 months in addition to orthopnea, exertional dyspnea and nocturia. On resin she developed constipation, decreased appetite and complained of increased weakness. However, she became edema-free and the rales in her chest disappeared. When she started to add extra salt in unmeasured amounts to her food, it became necessary to supplement the exchanger with a mercurial diuretic at approximately 2-week intervals.

Acidosis, Hyperchloremia, Hyponatremia, Hypokalemia and Hypocalcemia (Table II). In all of the subjects ingesting the resin in these amounts significant decreases in serum bicarbonate have developed. Two patients had greatly reduced bicarbonate values and hyperchloremia at the start, presumably because of previous ammonium chloride therapy. No one had symptoms which could be attributed to these changes. In seven patients hyperchloremia developed with chloride values of 106 mEq./L. or above. In four others values between 105 and 106 mEq./L. developed. The one patient without a rise had the serum sodium spontaneously rose to 138 mEq./L. in six weeks. D. R. had a low serum sodium before treatment which rose slightly to 137 mEq./L. seventeen days later. Inspection of the bicarbonate and chloride values again emphasizes the limitations of predicting sodium concentrations from changes in these anions and the need for determining the cation itself.[28] Only in J. R. was hyponatremia associated with symptoms. This patient started vomiting immediately after the onset of resin therapy but managed to retain most of her daily medication for a week. Her food intake however was

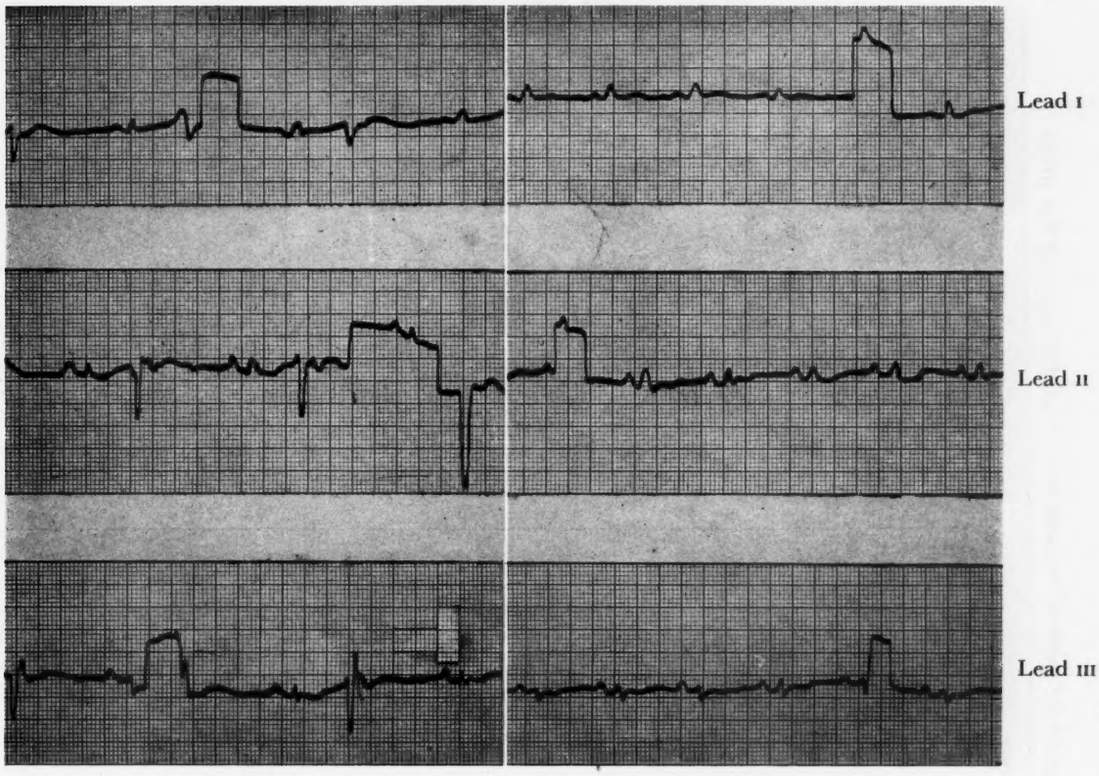

FIG. 7. Standard 3 limb leads of ECG during K^+ deficiency and after K^+ therapy in H. M. A, April 21st, obtained when serum K^+ concentration was 3.1 mEq./L; B, April 24th, after clinical response to KCl when serum K^+ was 3.7 mEq./L. The only difference is the ventricular irregularity during K^+ deficiency. The patient was not receiving digitalis.

markedly decreased. When seen at the clinic at the end of that week, she was extremely lethargic, weak and dehydrated, with evidence of sodium depletion. These symptoms were presumably a manifestation of a "low salt syndrome" since the serum sodium concentration was reduced to 125 mEq./L. and the blood non-protein nitrogen elevated to 51 mg. per cent. In addition a fecal impaction was present. The resin was discontinued and salt was added to her diet. Vomiting ceased but anorexia persisted. Four days later she had 2 plus edema of the ankles; the serum bicarbonate, sodium and chloride were returning to normal; and the blood non-protein nitrogen was lower. Nine days later she felt well; her appetite had returned. The edema had increased but the serum electrolytes and blood non-protein nitrogen were within the normal range. She was maintained thereafter on digitalis and salt restriction.

Hypokalemia with serum potassium concentrations below 3.5 mEq./L. developed in four patients (F. Vr., H. M., F. V., J. R.). Again these were patients who were not eating well at the time. In three others (R. L., M. F., A. C.) clear-cut decreases developed in serum potassium of 0.6 to 1.3 mEq./L. during resin therapy without hypokalemia. All of the patients with abnormally low serum potassium concentrations complained of weakness. Patient H. M. was shifted from the mixture of hydrogen and potassium form resins to hydrogen form alone because the former mixture was temporarily unavailable. Gastrointestinal distress with nausea and vomiting developed but the patient continued to take the resin. Within several days marked muscle weakness and lethargy appeared. He found it difficult to raise his arms or legs and frequently fell when attempting to walk. There was no difficulty in swallowing. Deep reflexes were present but depressed. His electrocardiogram was definitely abnormal, with many ventricular premature beats (Fig. 7A) but without findings specifically diagnostic of potassium deficiency. Arrhythmias, however, have been described as the sole electrocardiographic abnormality accompanying deficits of this cation.[29] The serum potassium value was

TABLE II

BLOOD AND SERUM FINDINGS IN PATIENTS RECEIVING 80:20 MIXTURES OF H^+ AND K^+ FORMS OF A CARBOXYLIC CATION RESIN

Subject, Age, Sex, Diagnosis	Time (days)	Resin (gm./days)	Blood NPN (mg. %)	Serum									Remarks
				HCO_3 (mEq./L.)	Cl (mEq./L.)	Na (mEq./L.)	K (mEq./L.)	Ca (mg. %)	P (mg. %)	TP (gm. %)	Alb. (gm. %)	Glob. (gm. %)	
C. M.	0	0	50	16.5	115.2	142	6.1	....	...	7.1	...	...	
47-F, RHD	7	45*	43	16.1	115.5	139	4.0	....	...	7.0	3.0	4.0	
	14	45*	38	15.9	111.8	143	4.2	9.4	4.4	...	...	...	
	28	45*	31	14.2	110.9	...	...	....	...	...	...	...	
	49	0	43	23.3	106.8	...	...	....	...	...	...	...	Nausea and vomiting; no resin days 48 to 60
	98	45†	50	23.5	104.4	...	...	10.1	4.6	...	...	...	
	147	60	36	16.6	109.1	144	5.2	....	...	...	...	...	
	182	60	47	19.8	108.3	141	5.4	10.2	3.3	6.7	3.6	3.1	
	294	60	44	25.1	99.8	...	...	10.5	3.5	7.2	3.5	3.7	
	409	60	52	12.4	111.9	134	3.8	8.9	5.0	7.6	3.8	3.8	
	444	60	44	16.9	107.9	138	4.5	....	...	6.8	3.5	3.3	
F. R.	0	0	34	16.5	110.3	143	4.8	....	...	7.9	3.3	4.6	
43-F, RHD	7	45*	33	26.3	106.7	151	4.8	....	...	...	...	...	Resin 6 days/week
	14	45*	47	16.6	102.0	...	...	....	...	...	...	...	
	21	45*	36	14.3	116.0	147	5.0	....	...	...	...	...	
	35	45*	44	19.8	.....	144	3.8	10.8	2.8	8.4	3.4	5.4	
	77	45	29	22.8	105.5	...	...	9.7	3.1	7.4	...	...	
	105	45	27	17.0	110.9	152	4.0	9.4	4.8	7.6	...	...	
	175	45	34	12.5	111.5	139	4.9	10.1	5.3	7.0	3.6	3.7	
	406	45	36	12.4	105.9	134	4.2	9.5	5.1	7.5	4.2	3.2	
F. Vr.	0	0	31	23.1	102.1	139	3.9	....	3.8	7.0	4.3	2.7	
26-F, RHD	12	45	46	14.7	94.0	130	4.5	....	...	...	...	...	
	57	45	36	19.2	105.0	137	4.1	10.4	4.0	7.7	4.9	2 8	
	127	45	34	23.2	98.3	138	3.2	10.3	3.4	7.0	4.5	2.5	Eating poorly
	155	45	27	20.1	100.2	141	3.4	9.6	3.8	6.9	4.3	2.5	Eating poorly
	179	45	34	19.2	96.1	134	3.2	8.4	4.0	7.0	4.1	2.9	Eating poorly
D. R.	0	0	29	26.6	103.6	134	5.5	....	...	...	...	...	
23-F RHD	17	45	29	21.1	105.7	137	3.7	9.7	3.4	7.9	4.2	3.7	
	32	45	32	21.2	93.6	...	5.9	....	...	...	...	...	
G. S.	0	0	26	24.4	97.9	...	...	....	...	6.9	...	...	
37-F, RHD	28	45*	28	31.2	98.0	142	4.3	10.5	2.8	6.0	2.6	3.3	No resin days 26 to 28
	91	45‡	32	25.4	103.1	133	4.0	10.7	3.4	7.4	2.8	4.6	
	112	45	26	25.1	96.5	146	5.2	....	...	...	...	...	No resin days 95 to 103
	126	45	25	21.1	110.5	142	3.7	9.9	4.0	7.4	3.3	4.0	
	203	45	27	22.2	93.2	151	4.3	10.8	3.9	7.8	4.4	3.4	
	308	45	26	23.0	104.4	148	4.1	10.8	4.4	7.3	...	...	
R. L.	0	0	44	28.7	101.4	145	5.0	....	...	7.5	3.1	4.4	
59-M, RHD	7	45	40	22.7	107.4	143	4.5	....	...	...	...	...	Unreliable intake
	14	45	37	22.5	109.6	144	3.7	9.2	2.4	5.6	2.7	2.9	Unreliable intake
	21	0	31	29.8	106.0	...	...	9.4	2.0	...	...	...	
H. M.	0	0	38	23.2	103.5	152	3.9	9.7	4.8	6.7	2.8	3.9	
45-M, HCVD; cor pulmonale	35	45	40	26.3	99.9	142	6.3	....	...	7.3	...	...	
	109	45*	43	22.8	100.1	142	2.4	10.9	4.0	7.4	4.0	3.4	H form started on day 105
	116	45*	46	17.0	100.7	143	3.1	11.4	4.4	7.9	3.5	4.5	Nausea and vomiting; clinical K deficit
	120	0	40	24.4	103.8	145	3.7	....	...	...	...	...	Extra KCl; improved
	151	45	36	24.2	101.6	140	3.5	....	3.6	7.1	3.8	3.3	
	182	45	34	24.4	105.1	149	3.4	8.8	4.4	6.6	3.6	3.0	
	219	30	40	28.4	95.8	140	4.1	8.9	3.5	6.8	3.5	3.3	

TABLE II—(*Continued*)

Subject, Age, Sex, Diagnosis	Time (days)	Resin (gm./day)	Blood NPN (mg. %)	Serum									Remarks
				HCO_3 (mEq./L.)	Cl (mEq./L.)	Na (mEq./L.)	K (mEq./L.)	Ca (mg. %)	P (mg. %)	TP (gm. %)	Alb. (gm. %)	Glob. (gm. %)	
S. H.	0	0	...	26.3	95.7	...	...	10.4	4.4	7.6	3.7	3.9	
52-F, HCVD	38	45	50	19.4	107.1	146	4.4	....	...	...	...	...	
	52	45	44	20.4	107.7	154	4.6	....	...	...	...	...	
	102	45	42	16.8	112.2	142	4.4	10.8	4.2	7.4	...	...	
	129	45	43	21.7	108.1	140	4.0	10.4	3.5	7.6	4.6	3.0	
	161	45	43	23.2	107.0	147	5.2	10.2	3.1	6.9	...	...	
	293	45	55	15.8	111.3	138	3.7	9.4	3.8	7.0	3.6	3.4	
	335	45	43	17.5	104.6	140	4.0	9.3	3.9	7.2	3.5	3.7	
F. V.	0	0	37	26.0	112.8	148	4.8	9.4	3.1	7.0	3.2	3.7	
71-M, Art. and HCVD	21	45	36	28.7	107.1	...	...	9.7	2.6	6.6	3.6	3.0	
	56	45	34	22.1	113.0	139	3.8	9.8	2.9	6.3	3.9	3.4	
	112	45	34	20.9	105.3	141	4.1	9.7	2.4	6.4	2.5	3.9	
	140	45	35	28.1	101.0	...	...	10.3	2.5	5.8	3.0	2.8	Resin decreased
	182	45	38	19.3	112.7	150	...	9.9	2.3	6.8	3.4	3.4	
	210	45	34	19.5	109.7	...	...	10.4	2.2	6.5	3.4	3.1	Anorexia
	266	45	38	18.9	109.4	145	3.0	10.2	2.3	6.4	3.5	2.9	Weak, tired
	335	45	36	....	108.0	148	3.6	8.9	2.8	5.6	3.1	2.5	Weak, tired
	356	60	25	14.1	114.4	141	3.2	8.7	2.2	6.3	3.2	3.1	Weak, tired
	359	60	34	16.8	114.6	144	3.6	8.8	2.4	6.0	3.0	3.0	K citrate 2 days
	362	60	37	15.7	108.1	142	3.8	7.5	3.1	...	...	...	K citrate 3 days
M. F.	0	0	39	....	.....	139	4.9	10.2	4.3	8.2	3.2	5.1	
41-F, HCVD	17	45	28	21.7	105.4	143	3.8	9.6	2.9	7.1	3.2	3.9	
	94	45	31	20.8	104.6	141	4.1	9.3	3.2	6.8	3.5	3.3	
J. R.	0	0	31	24.5	98.9	134	3.8	10.1	2.4	6.0	3.3	2.7	
68-F, Art. CVD	7	45	51	9.0	107.2	125	3.9	....	...	7.8	...	...	Nausea and vomiting; clinical Na deficit
	11	0	47	15.7	102.3	135	2.6	....	...	7.0	3.7	3.3	Anorexia
	20	0	32	24.1	103.2	135	3.0	....	...	5.9	3.3	2.6	
A. C.	0	0	36	26.6	100.6	140	4.3	10.4	3.8	7.0	3.8	3.2	
62-F, Art. and HCVD	56	45	43	17.6	100.0	144	3.7	10.3	3.4	7.9	3.3	4.6	

* H form resin
† 80:20 H^+, K^+ mixture started on 63rd day
‡ 80:20 mixture started on 42nd day

reduced to 3.1 mEq./L.; it had been 2.4 the preceding week. The resin was temporarily discontinued and the patient received 0.6 gm. potassium chloride orally after each meal and at bedtime. He noted a dramatic increase in his strength after the third dose. A subsequent electrocardiogram revealed a regular rhythm but was otherwise unchanged. (Fig. 7B.) The hydrogen, potassium forms of the exchanger were subsequently restarted without adverse effects. F. Vr. and F. V. decreased their food intake but continued to ingest the resin; neither one vomited. Despite the potassium supplied by this mixture of resin forms F. Vr. was found to have a serum potassium of 3.2 mEq./L. on the 127th day and F. V. of 3.0 on the 266th day of treatment. No definite symptoms of potassium deficiency were apparent. F. V. received supplementary potassium citrate 6 gm. per day in divided doses without relief of weakness, although the serum potassium rose to normal concentrations. J. R., in whom hyponatremia had developed, was found to have hypokalemia, with a serum potassium of 2.6 mEq./L., as renal function improved. Normal levels of serum potassium returned after withdrawal of the resin and resumption of an adequate diet. The three patients with decreases in serum potassium without hypokalemia had no clinical findings indicating potassium deficits.

Serum calcium concentrations were within the normal range in the patients in whom this cation was measured at the start of therapy. In four patients (C. M., F. Vr., H. M., F. V.) abnormally low calcium values (below 9.0 mg. per cent) developed during prolonged treatment, without clinical findings. The low values were encountered at 409, 179, 182 and 335 days, respectively. In three other patients (F. R., S. H., M. F.) decreases of 0.9 to 1.3 mg. per cent were recorded during treatment. No evidence of tetany was observed. Serum inorganic phosphorus and protein values did not change significantly during treatment.

Three patients (C. M., R. L., S. H.) had slightly elevated non-protein nitrogen concentrations prior to resin therapy. In R. L. the value returned to normal during treatment. Temporarily elevated levels during ingestion of the exchanger developed in five others (F. R., F. Vr., H. M., J. R., A. C.).

The few recorded urinalyses did not reveal the development of any new urinary abnormalities during therapy. One patient, M. F., who had 3 to 4 plus albuminuria while on mercurial diuretics became albumin-free while on resin therapy.

No patient with hypertension had a significant decrease in blood pressure.

COMMENTS

The cation exchange resins provided a useful supplement to the therapy of these patients with congestive heart failure when digitalis, sodium restriction and limited activity were not sufficient to maintain them edema-free. The resin supplanted the mercurial diuretic and ammonium chloride which eight of the subjects had required at one- to two-week intervals previously. It was clear in two patients, however, that the exchanger was not as effective as the mercury and that it may be necessary at times to supplement the resin with the latter. Data obtained in these and related studies indicate that this clinical effect was mediated only partly through increased fecal excretion of sodium and probably mainly through the acidifying effect of the resins. The latter necessitates precautions similar to those employed when ammonium chloride is continuously administered, if the dangers of an uncompensated acidosis are to be avoided. In addition they indicate that forms of the resin which do not act as diuretics will be even less effective than these in the therapy of edema unless their efficiency in binding sodium is greatly increased.

In none of the patients did it prove possible to liberalize significantly or abandon sodium restriction. Theoretically this would be the great advantage of resin therapy. An analysis of our previous stool data and of those published by others, however, reveals the limited efficiency of these substances. Our data indicate that an average of 0.74 ± 0.62 mEq. of sodium per gram of carboxylic cation exchange resin in the hydrogen or ammonium forms will be excreted in the feces if a full diet containing the usual amount of sodium is eaten; seldom is more than 1.3 mEq./gm. removed.[1–3,8] This is in agreement with the data of others.[4,10,12,15,16] Hence at this level of salt intake 45 to 60 gm. of resin per day would be needed to remove 30 to 40 mEq. of sodium from the diet. At first thought this would seem to indicate that the diet might be liberalized by 2.0 gm. (35 mEq.) of sodium chloride per day. Unfortunately the sodium binding properties of these preparations decrease with a decreasing

sodium intake.[6,7,15,16,23,30] In addition, substituting the potassium form of the resin for part of the hydrogen or ammonium forms reduces the exchange capacity.[1–3,8,12] For example, the exchangers bind on the average only 0.3 ± 0.25 mEq. of sodium per gram of resin if dietary sodium is limited to 200 mg. (9 mEq.) or less per day.[15,16,30] Diets such as this therefore could be liberalized by only 400 mg. (17 mEq.) of sodium per day if the same amount of resin were ingested. There can be little doubt that the acidifying diuretic effect of these resins aids substantially in controlling edema.

Even though the incidence of gastrointestinal symptoms was fairly high, they were not an insurmountable obstacle to continued treatment. Eight of these patients have been on resins for 150 to 451 days. Only two patients of the present series were taken off exchangers because of adverse clinical reactions. Two others were discontinued because they no longer required resin therapy.

The biochemical abnormalities, however, which have developed in all of these subjects may preclude long-term therapy in the present manner. Abnormally low serum concentrations of either sodium, potassium or calcium developed in seven of the patients, with the majority having multiple abnormalities. When the two patients with actual vomiting are excluded, it is apparent that these are complications of long-term therapy. For example, hyponatremia was observed between the 91st and 409th day; hypokalemia between the 127th and the 266th day; and hypocalcemia between the 179th and 409th day. There is also a clear warning in the present data of the dangers in resin therapy to subjects who do not eat or in whom vomiting or other conditions develop which in themselves tend to produce sodium and potassium losses from the body. Such subjects are prone to develop both sodium and potassium deficiencies as well as severe acidosis. The amount of potassium supplied in the present "80:20" mixture of hydrogen and potassium forms of the resins is not enough to prevent the development of hypokalemia without adequate dietary intake of food which contains potassium. There is no apparent reason to doubt that similar mixtures of ammonium and potassium forms of the exchanger will produce similar effects.

Aberrations of sodium and potassium metabolism during therapy with the exchangers, however, are much more easily solved than the one involving calcium. The data indicate that calcium depletion in human beings is probably a concomitant of long-term resin therapy. This was not unexpected since the affinity of these resins for calcium has been well recognized.[1,6,10,22,23] Hypocalcemia with tetany has been reported after relatively short therapy with the sulfonic forms of cation exchangers[15] but it had not been shown to be a problem with the carboxylic cation exchangers until the present. Significant increases in excretion of calcium via stool or urine during carboxylic resin therapy presumably have not been demonstrated in patients because it must be a small daily increment which becomes important only with prolonged therapy and relatively low calcium intakes. It seems likely that others would have encountered similar changes if their therapy had been as prolonged as in the present series with frequent serum analyses for calcium. McChesney's data in rats demonstrate that it is possible to increase the fecal excretion of calcium to amounts surpassing the intake during the administration of (1) the hydrogen form of the carboxylic exchanger, or (2) "80:20" mixtures of ammonium and potassium carboxylic resins, or (3) the hydrogen form of the sulfonic exchanger. Calcium excretion in the stool of these animals was increased by 0.07 to 0.43 mEq./gm. of administered carboxylic exchanger. Even larger amounts were bound by the sulfonic resin. Similar negative balances of iron and magnesium were demonstrated.[10] The low calcium intake provided by the limited diets these patients ingested probably played an important role in this development. Milk was restricted to 200 ml. a day. It is a safe assumption, also, that calcium levels in the serum were not lower and no clinical evidence of tetany was observed because the bones were supplying calcium to the extracellular fluid. The acidosis which accompanies this therapy would favor the exchange and might also increase the amount of ionized calcium in the serum.[31] Coincident hypopotassemia would also mask clinical findings of tetany.[32] The dangers of calcium depletion include not only the abrupt events occurring with increased neuromuscular sensitivity and tetany but also osteoporosis with increased susceptibility to fractures. The addition of calcium to the diet may prevent calcium depletion. However, if large amounts of supplementary

calcium are ingested, the resin will presumably bind it preferentially to sodium, thereby cancelling the effectiveness of the resin since it will not interchange again with sodium in the intestinal tract.[1] The calcium would have to be supplied at a time when the resin was not available for exchange. It is possible to supply more calcium than these patients ingested and still maintain the activity of the resin by including dialyzed milk in their intake. It is not established, however, that this will supply sufficient calcium. An effective but not very practical manner to supply this cation and retain the effects of the resin would be to inject intravenous calcium gluconate or lactate at intervals. A third possibility would be to administer the exchangers intermittently. In any event the magnitude of the problem may be expected to increase as uninterrupted resin therapy is prolonged, and it may prove to be an important obstacle to long-term use of the substances presently available.

All patients receiving resin therapy must be carefully observed, but this is a necessary requirement in congestive heart failure irrespective of therapy. It would seem wise to carry out blood and serum analyses for non-protein nitrogen, carbon dioxide, chloride, calcium, phosphorus and, if possible, sodium and potassium at intervals during the course of treatment. The difficulties in detecting abnormalities of the latter two ions from corollary data alone are clear. Although it is probably not necessary to suggest a rigid schedule for this, a satisfactory plan would call for weekly or biweekly measurements during the first month and then monthly analyses. It is worth emphasizing that, if our data are representative, there is little reason to expect trouble before six months have elapsed, provided the patient does not have renal disease, is eating adequately, and is not depleted of minerals at the onset of treatment. If adverse findings appear, the resin should be discontinued, at least temporarily.

The final role of the carboxylic cation exchange resins in the therapy of edema is not yet established. They do minimize the need for mercurial diuretics but it is not yet clear whether sodium restriction should preferably be supplemented by oral diuretics such as urea or ammonium chloride, or by resin. Sodium restriction is necessary with both types of treatment. In general any medication which prevents edema is to be preferred to one which acts only after fluid retention has occurred. If mercurial diuretics are necessary, it would seem simpler to potentiate their action with intermittent ammonium chloride rather than with resin. At present the choice of therapy is best decided on an individual basis considering such factors as palatability, ease in taking medication, reaction of patient, cost, renal disease, success with other regimens and, lastly, the availability of adequate biochemical laboratory facilities. It must be kept in mind too that adequate control of edema by digitalis, sodium restriction and relative rest makes the use of supplementary diuretics or resins unnecessary. Finally, if the efficiency of the resins as well as their specificity could be improved significantly, many of the problems which have been recognized in the course of this study would not occur and liberalization of the dietary intake of sodium would be possible.

SUMMARY

1. Twelve patients with congestive heart failure have been treated with 30 to 60 gm. per day of a carboxylic cation exchanger, 80 per cent in the hydrogen and 20 per cent in the potassium forms, for intervals up to fifteen months in length. These resins provided a relatively safe supplement to the basic therapy for approximately six months. Thereafter hyponatremia, hypopotassemia and hypocalcemia were frequently observed. The problem of hypocalcemia may prove to be a significant obstacle to longer, safe therapy with these materials.

2. The exchangers did not permit significant liberalization of dietary sodium. The aforementioned findings indicate that an increase in the efficiency and specificity of the presently available exchange resins is necessary if they are to serve their uniquely favorable advantage of harmlessly liberalizing the intake of sodium in patients with edema.

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Metabolic Studies on the Effects of Ion Exchange Resins in Edematous Patients with Cardiac and Renal Disease*

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The role of sodium retention in the pathogenesis of edema in patients with cardiac or renal disease is well established. With certain exceptions[1,2] the fluid retained in such patients, as reflected by change in weight, can be satisfactorily explained in terms of sodium balance.[3] Consequently, considerable therapeutic success in the control of edema has been achieved by regimens which involve severe restriction of the sodium intake and/or promotion of urinary excretion of sodium by the administration of diuretics.

However, for various reasons, the maintenance of satisfactory sodium restriction may be difficult for some patients. Furthermore, since the natural history of cardiac disease usually involves a gradual diminution in myocardial efficiency, the patient who at first may be controlled by digitalis and moderate salt restriction ultimately may require periodic mercurial diuretics despite progressive limitation of physical activity. As myocardial deterioration continues there is an intensification of all the factors contributing to sodium retention in congestive failure and, finally, the patient may no longer respond adequately to mercurial diuretics, even after pre-treatment with ammonium chloride.[4] Under these circumstances, despite sharply reduced sodium intake, increasing edema will lead to the familiar terminal picture of general anasarca.

For these reasons the use of orally administered ion-exchange resins, which can remove sodium and other cations from the gastrointestinal tract, was suggested for the treatment of edematous patients.[5] Since then a number of reports describing this clinical application have appeared.[6–11] However, these do not include many extensive, controlled metabolic studies on edematous patients. The few metabolic studies available suggest that it may be difficult to achieve negative sodium balance and satisfactory mobilization of edema in patients treated with resins on low salt diets.[8,12,13]

The present communication summarizes metabolic observations on a group of patients with cardiac and renal edema which was successfully mobilized by the administration of a cation exchange resin. The results demonstrate that significantly negative sodium balances may be achieved with these agents in patients on a low salt diet. Moreover, these studies suggest that, provided certain precautions are observed, the hyperchloremic acidosis produced by the removal of sodium from the gastrointestinal tract without chloride, which must subsequently be excreted by the kidneys, is not an absolute contraindication to the use of resins by hospitalized patients with renal disease.

METHODS AND MATERIALS

The eleven patients in this series included five with uncomplicated rheumatic heart disease, three with rheumatic heart disease complicated by arteriosclerotic or hypertensive renal disease, one with rheumatic heart disease and diabetic intercapillary glomerulosclerosis, one with nephrotic syndrome of unknown etiology, one with

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nephrotic syndrome secondary to multiple myeloma.

All were maintained on a metabolic ward on a low salt diet. Calculation of food intake was based on repeated analyses of daily aliquots of the diet. For these extended periods of study two diets of approximately equivalent content of sodium, chloride, potassium, phosphorus, nitrogen and calories were given on alternate days. After appropriate control periods varying quantities and combinations of the several ion-exchange resins used in carbo-resin®* were administered as suspensions in water. Generally, the daily dose was divided into four equal portions, one part being administered after breakfast and at 3 P.M., and two parts after the noon meal. This procedure was adopted to alleviate the nocturnal abdominal distress experienced by some patients when a dose was given after the evening meal. The duration of resin therapy and the specific doses will be indicated subsequently.

Patients were weighed daily shortly after the early morning urine collection. Daily urines and stools, pooled for three- to six-day periods, were refrigerated until analyzed. At the beginning of each stool collection period, or more frequently as required, venous blood was drawn without stasis, and venous pressure and circulation time (ether and decholin) were determined.

Urinary excretion of creatinine, urinary and fecal excretions of sodium, chloride, potassium, phosphorus, nitrogen and, in some patients, fecal calcium excretion† were measured. The corresponding blood or serum constituents, and serum total protein and A/G ratios, uric acid, bicarbonate, and blood eosinophil counts also were determined.

The chemical methods employed for analyses of blood, urine or ashed samples of diets, stool or vomitus were as follows: Sodium and potassium by means of a lithium internal standard flame photometer;[14] chloride by Van Slyke's modification of Sendroy's iodometric method;[15] nitrogen by a micro-Kjeldahl distillation, and titration technic;[16] phosphorus by the method of Fiske and SubBarow;[17] creatinine by Peters' modification of the Folin-Wu technic;[18] total protein by micro-Kjeldahl distillation and titration,[16] with separation of albumin and globulin by use of 21 per cent sodium sulfite;[19] serum CO_2 by the manometric method of Van Slyke and Neill;[20] calcium in the stool by the method of Kramer and Tisdale;[21] eosinophil counts on heparinized blood by the method of Randolph.[22]

* Carbo-resin (sodium-removing resin, Lilly) is a mixture containing 88 per cent of the carboxylic acid cation exchanger, amberlyte XE-64, which is a cross-linked acrylic acid polymer, ⅔ in the hydrogen cycle and ⅓ in the potassium cycle, plus 12 per cent of an anion exchanger, Rohm and Haas alkylene polyamine resin, XE-58. The usual commercial form of carbo-resin® and individual lots of the separate ion exchange resins in the mixture were supplied through the courtesy of Dr. Kenneth G. Kohlstaedt, of Eli Lilly & Company.

† We are grateful to Mrs. Judy Bellin of Dr. Daniel Laszlo's Neoplastic Research Laboratory, Montefiore Hospital, for the calcium determinations.

RESULTS

The pertinent data on eight of the eleven patients are presented in conventional Albright-Reifenstein[23] metabolic charts.* (Figs. 1 to 8.)

The first chart presents the data on Patient S. G., a forty-three year old man with rheumatic heart disease (mitral stenosis and insufficiency and aortic stenosis) in chronic congestive failure, who entered the hospital with severe dyspnea and marked anasarca resistant to the usual therapy. His pulse rate was rapid and markedly irregular; the electrocardiogram showed auricular fibrillation with rapid ventricular rate and multiple ventricular extrasystoles which were considered evidence of digitalis toxicity; venous pressure was 23 cm. of water.

After a five-day control period he was given a mixture of 40 gm. of resin in the acid cycle plus 20 gm. in the potassium cycle. He had a tenfold increase in fecal sodium excretion, an increase in urinary volume and chloride excretion and a progressive decrease in body weight. During the first six days on this regimen his average daily fecal sodium excretion was 67 mEq. per day, and his sodium balance was negative to the extent of 50 mEq. per day. In twelve days of

* Daily intake is plotted downward from the zero or base line. Superimposed on intake from below up is the daily excretion in stool (open boxes), urine (diagonal cross-hatched boxes) and vomitus (dotted boxes), respectively. When output is less than intake the resulting positive balance is reflected by the open area below the base line. Conversely, when output exceeds intake the negative balance will be represented by the rise of the daily boxes above the base line. Serum electrolyte concentrations and blood urea nitrogen levels for the corresponding days are superimposed over the respective balances. Venous pressures and body weights are given at the top of each chart whereas blood eosinophil counts and other pertinent data on medications, etc., are presented at the bottom.

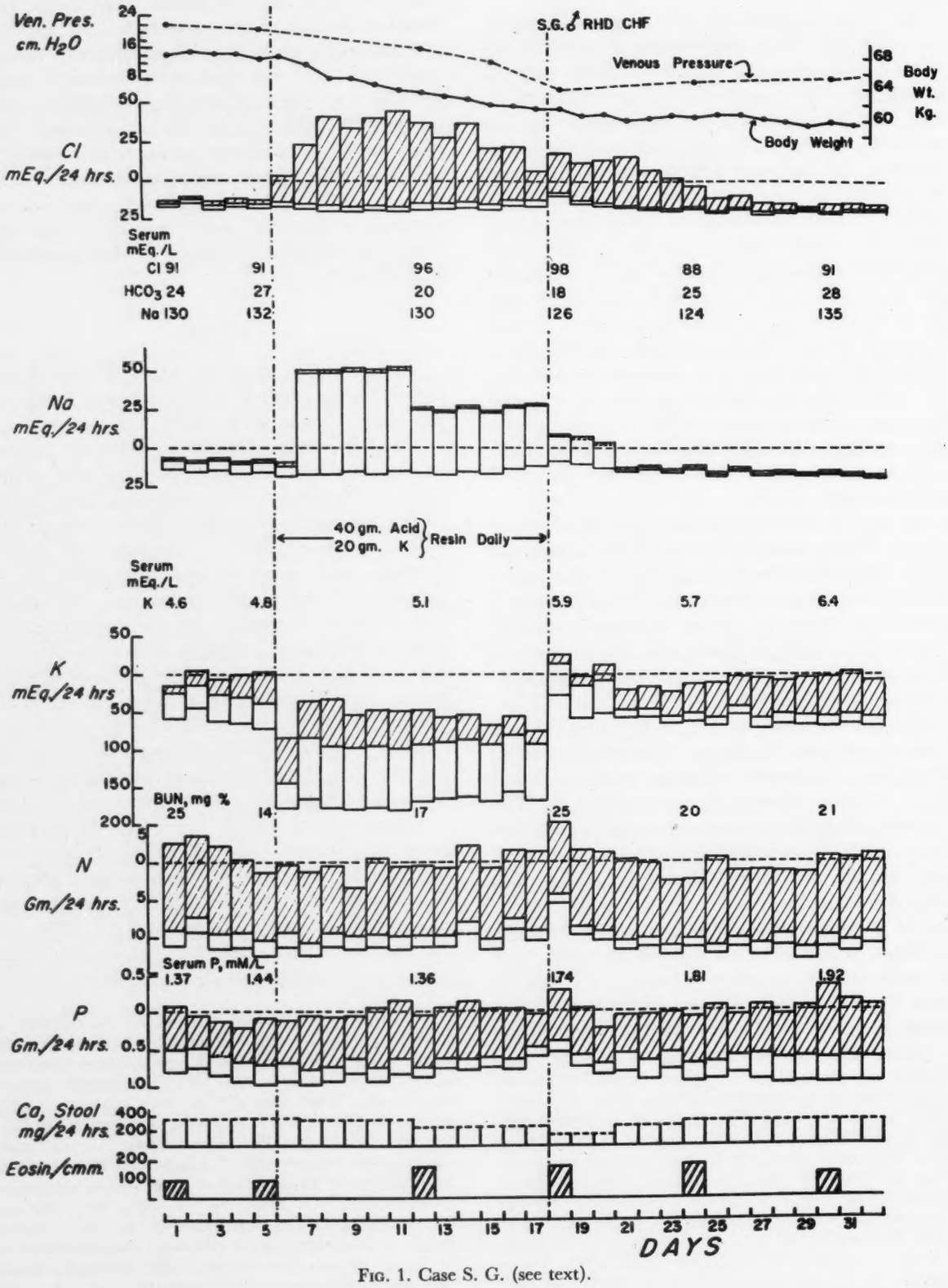

FIG. 1. Case S. G. (see text).

resin therapy his weight dropped from 68 kg. to 61 kg., with marked symptomatic improvement.

Six days after beginning resin therapy, although urinary chloride excretion had significantly increased, his serum chloride had risen from 91 to 96 mEq./L. with a corresponding fall in serum bicarbonate and no change in serum sodium. Six days later, when resin therapy was stopped, serum chloride was 98 mEq./L., bicarbonate 18 mEq./L., and serum sodium had fallen to 126 mEq./L. Three days after resins were discontinued the fecal sodium excretion dropped to the control levels. The increased urinary chloride excretion, however, persisted and six days later, after his body weight had decreased another kilogram, his serum chloride, bicarbonate and sodium were 88, 25 and 124 mEq./L., respectively. Urinary chloride excretion then gradually diminished without any specific therapy and within six days his serum electrolytes returned to control levels.

The changes in potassium balance observed in this patient are of particular significance. During the control period he was in potassium balance. The administration of the carbo-resin, containing resin in the potassium cycle, resulted in a marked increase in his potassium intake. However, after an initial increase during the first day his urinary potassium excretion gradually declined and, despite the increase in fecal potassium excretion due to the resin, he remained in markedly positive potassium balance, retaining a total of 665 mEq. in twelve days. During this period the patient tolerated increased dosage of digitalis without the marked electrocardiographic evidence of toxicity previously observed, and adequate digitalization was achieved in the next few days. Subsequently, he was subjected to mitral valve commissurotomy without incident.

The urinary potassium excretion remained low in the first three-day period after resins were withheld. Subsequently, potassium balance was achieved as fecal potassium excretion dropped and urinary excretion gradually increased. The serum potassium level, which averaged 4.7 mEq./L. in the control period, rose during and even after cessation of resin therapy. There were no particularly striking changes in nitrogen or phosphorus balances or fecal calcium excretion. With the development of acidosis during resin therapy, however, urinary phosphorus excretion tended to increase.

Figure 2 illustrates the effects of ion exchange resins in Patient E. S., a forty-five year old woman in severe chronic congestive failure secondary to rheumatic mitral valvular disease. On admission her principal manifestations of failure were extensive accumulation of fluid in her lower extremities and abdomen, and venous pressures of 24 to 28 cm. of water. Her weight was approximately 68 kg.; her eosinophil count was depressed; her serum electrolytes, blood urea nitrogen and serum phosphorus were within the normal range; and her sodium, chloride, potassium, nitrogen and phosphorus balances were slightly positive.

When the patient was given 40 gm. of resin in the acid cycle plus 8 gm. of the anion exchanger daily, there was a prompt increase in fecal sodium excretion, with corresponding increases in urine volume and decrease in weight. Urinary chloride excretion progressively increased until, by the fifth day, it approximated the sodium removed in the stool by the resin. However, the serum chloride concentration rose and the serum bicarbonate level fell and remained low. The markedly negative sodium and chloride balances were maintained throughout the course of resin administration, during which a 10 kg. weight loss occurred. After the initial fall in body weight there was a parallel fall in venous pressure which eventually reached a constant level of 8 cm. of water.

In contrast to the persistent, negative sodium balance while on the resin and low salt diet, potassium balance remained negative for only a few days, although no potassium cycle resin or other supplementary source of potassium was given. With the progressive increase in fecal potassium excretion there was a gradual decrease in the urinary potassium excretion, which finally declined to less than 1 mEq. daily. The initial fall in urinary potassium excretion was not accompanied by significant reduction in serum potassium level. However, by the thirteenth day of resin therapy the serum potassium level was only 2.79 mEq./L. and, partly as a consequence of decrease in food intake, the potassium balance was transiently negative. Addition of 20 gm. daily of resin in the potassium cycle to the mixture led to a positive potassium balance for six days, despite some increase in fecal excretion of potassium. However, there was no change in either the serum potassium level or the very low urinary potassium excretion.

After resin therapy was stopped, fecal potassium excretion decreased but remained above

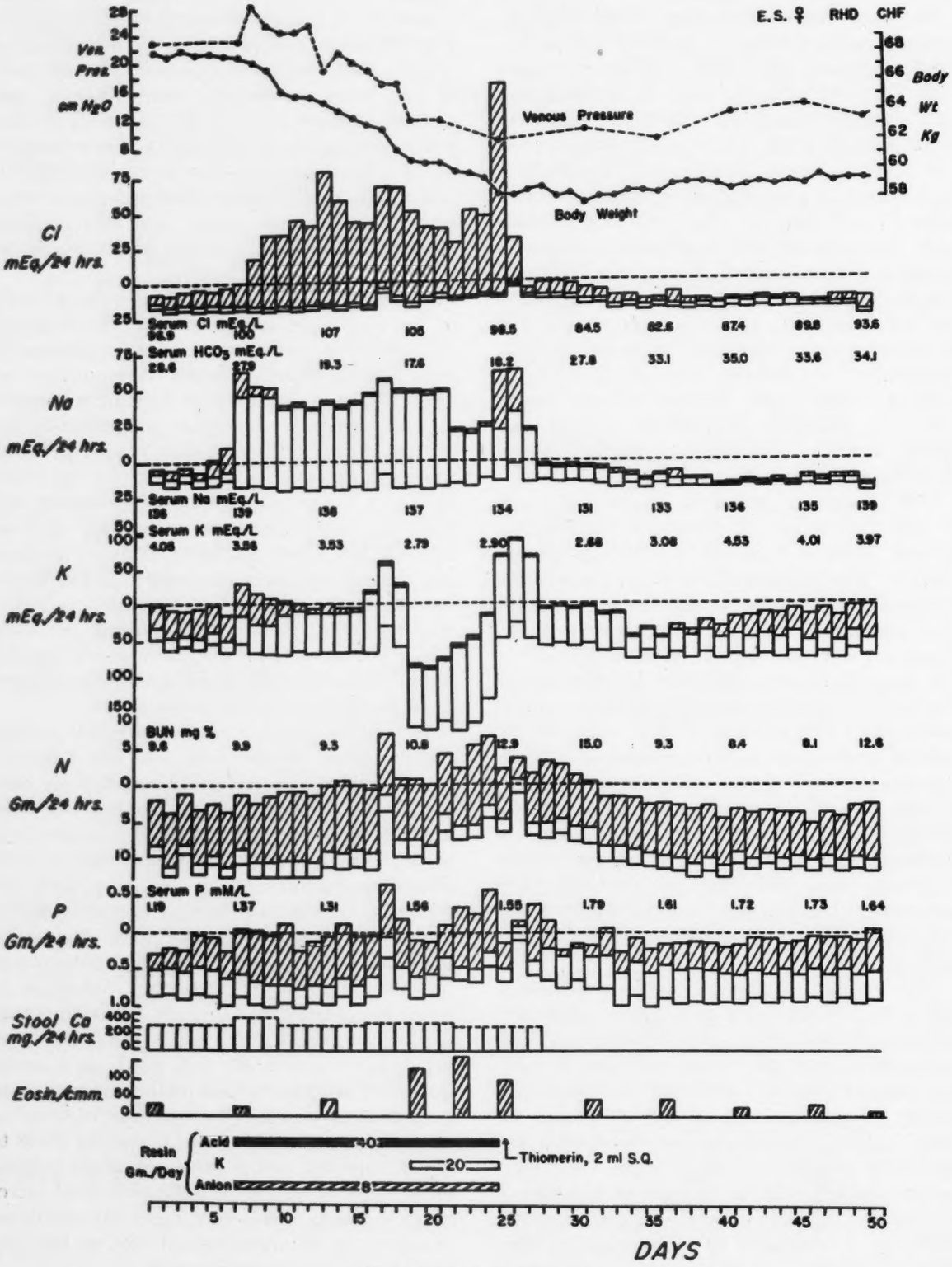

FIG. 2. Case E. S. (see text).

control levels for nine days. Yet, urinary potassium excretion did not increase significantly until the serum level exceeded 3 mEq./L. At this point there was a gradual increase in urinary potassium excretion with a concurrent rapid rise of the serum potassium level toward normal. But the patient continued to exhibit persistent hypochloremic alkalosis, suggestive of intracellular potassium depletion, which continued until the potassium intake was supplemented by oral potassium salts several weeks later.

On the day resin therapy was stopped an injection of a mercurial (thiomerin®) produced profuse chloruresis, significantly less natriuresis, but no change in urinary potassium, nitrogen or phosphorus excretion. Thereafter urinary chloride excretion dropped and remained below control levels throughout the period of hypochloremic alkalosis. Following the mercurial diuresis there was a fall in serum chloride and an equivalent rise in serum bicarbonate.

During resin therapy the serum sodium level declined slightly. The lowest value, 131 mEq./L., was observed six days after discontinuing resin therapy, when the increased fecal excretion of sodium had subsided. Without specific therapy the serum sodium concentration returned to the control level within three weeks.

It is interesting that the blood urea nitrogen in this patient rose progressively during the course of the resin therapy but fell sharply after resins were discontinued. This was associated with parallel changes in plasma creatinine level suggesting a significant fall in glomerular filtration rate. No significant changes in fecal calcium, nitrogen, phosphorus or chloride excretion occurred during administration of acid resin plus the anion exchanger.

When resins were started the eosinophil count of this patient, who was in severe congestive failure, was markedly reduced. At the end of the resin administration period her eosinophil count had risen to normal levels but subsequently dropped to the previously low level. At this time she was again in markedly positive sodium and chloride balance with virtually no sodium or chloride appearing in her urine.

Figure 3 illustrates the intermittent administration of resin, with and without the anion exchanger, to M. F., a sixty year old woman with rheumatic and arteriosclerotic heart disease whose massive anasarca could not be mobilized by mercurials, even after pre-treatment with ammonium chloride. Unfortunately, administration of resin to this patient led to the development of fecal impaction with a consequent continuous "overflow" diarrhea. Although loss of diarrheal stool made stool collections incomplete, fecal excretions are reported for comparison with the changes in urinary excretions, blood chemistries and body weight.

When 40 gm. of resin in the acid cycle and 20 gm. in the potassium cycle were given for four days, there was an increase in fecal sodium excretion, leading to negative sodium balance. However, the increase in urinary chloride excretion was insufficient to compensate for the sodium loss, leading to acidosis, as manifested by the rise in serum chloride and the fall in bicarbonate. During this period there was a 6 kg. weight loss.*

After withdrawal of resins fecal electrolyte excretion returned to normal and she was again in positive sodium and potassium balance with very little sodium or potassium in the urine. However, the increased chloride excretion persisted and, seven days later, serum chloride level had declined to 92 mEq./L. and the bicarbonate and sodium levels rose.

At this point the same dosage of acid and potassium resins plus 8 gm. of the anion exchanger was given daily for six days. Urinary chloride excretion promptly increased for two days, then declined to the control level. Again she developed fecal impaction and incontinence. The incomplete collections revealed increased fecal excretion of sodium. By the end of this period she had lost about 2 additional kg., serum sodium and chloride levels had not changed, and serum bicarbonate again had fallen to 18 mEq./L. With cessation of resin therapy urinary chloride excretion dropped to the control level, fecal sodium excretion decreased, but fecal potassium excretion remained elevated. Concurrently, potassium virtually disappeared from the urine and serum potassium fell to 3.7 mEq./L.

Six days later resin therapy was again started. Electrolytes had returned to control levels, with sodium and bicarbonate somewhat higher than at the start of the study. Commercially available carbo-resin was now administered. Fecal sodium excretion promptly rose and remained elevated. During this period constipation was prevented by the oral administration of a methyl cellulose

* This disproportionately large weight loss suggests that urinary, as well as fecal, incontinence was present, and made urine collection incomplete.

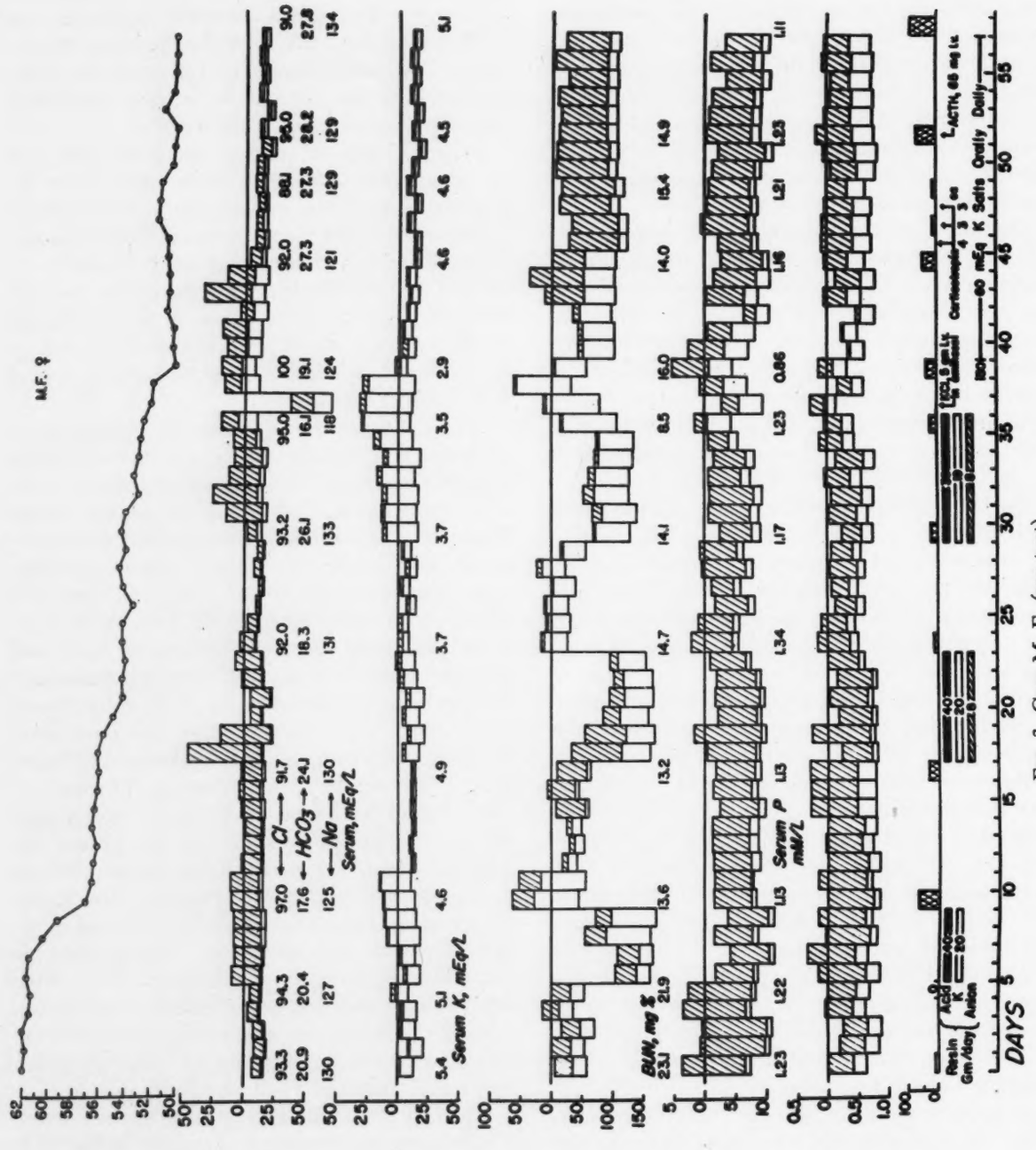

Fig. 3. Case M. F. (see text).

preparation and the stool collections were complete. Despite the apparently markedly positive potassium balance, urinary potassium excretion and serum electrolyte concentration remained low. At the end of resin therapy serum sodium and bicarbonate had fallen to 118 and 16 mEq./L., respectively, and the serum chloride had increased somewhat. After stopping resin therapy weight loss continued, serum sodium rose slightly and bicarbonate and chloride returned to more normal levels. Subsequently, when the patient's food intake was maintained, organic potassium salts administered orally, and adrenocorticotropin given for four days, her serum sodium gradually returned to 133 mEq./L.

In this patient no effect of the anion exchange resin on chloride, phosphorus or nitrogen excretion was observed. It should be noted that with the persistently severe congestive failure this patient's eosinophil count remained low throughout the period of study.[24] With the mobilization of edema fluid there was a rather prompt decrease in the blood urea nitrogen from 23 to 13.6 mg. per cent. Subsequently, she was discharged from the hospital on intermittent resin therapy.

Figure 4 illustrates the successful mobilization of extracellular fluid in a fifty year old man (A. D.) with rheumatic heart disease, who had recently recovered from subacute bacterial endocarditis and was not readily controlled by conventional therapy. It illustrates also the ability of such a patient to tolerate an increased intake of sodium while maintained on resins.

In the control period, despite rigid sodium restriction, he continued to retain fluid. Although he developed no gross edema, his venous pressure was elevated. When first placed on a resin mixture containing 40 gm. in the acid cycle, 20 gm. in the potassium cycle, and 8 gm. of the anion exchanger daily for five days, he experienced severe gastrointestinal irritation leading to anorexia, nausea and vomiting. As a consequence of increased fecal excretion of sodium his sodium balance became negative. As a result he lost 5 kg. of body weight, and his venous pressure fell. In consequence of chloride loss in vomitus, at first, there was slight and later only moderate increase in urinary chloride excretion. At the termination of this course of resin therapy serum sodium level had not changed, serum chloride concentration had risen to 103 mEq./L., and the bicarbonate had fallen to 18.1 mEq./L. During the following six days urinary chloride excretion gradually declined almost to the control level. Fecal sodium excretion, however, still remained high, indicating persistence of resin in the gastrointestinal tract.

Six days later body weight had increased 1.3 kg. When resin therapy was now re-instituted he experienced no gastrointestinal difficulty. Prompt increase in fecal excretion of sodium again led to negative sodium balance and an additional 2.5 kg. decrease in weight. Venous pressure remained at 6 cm. H_2O. After six days on the resin the serum sodium level fell to 129 mEq./L., and bicarbonate and chloride were 15.4 and 103 mEq./L., respectively. At this time 1 gm. (17 mEq.) of sodium chloride in the form of a compressed salt tablet was given with each meal. During the next three days, due to delayed excretion of resin, there was a falsely high, positive sodium balance without gain in weight. The increased urinary chloride excretion without fall in serum chloride suggests that even in this period there was increased resin uptake of sodium from the gastrointestinal tract. This was definitely reflected in the rise in fecal sodium excretion in the next six-day period. Urinary excretion of chloride continued to increase, and the patient remained in slightly negative sodium balance and in significantly negative chloride balance.

After four days of increased sodium chloride intake serum chloride concentration rose somewhat and the serum sodium level was unchanged. After nine days, when administration of both resins and sodium chloride was discontinued, serum sodium, chloride and bicarbonate levels were 135, 109 and 20.6 mEq./L., respectively. For the next six-day period sodium content in the pooled stools was still elevated and urinary chloride excretion gradually fell to control levels. Three days later serum electrolyte levels were normal. During resin therapy the blood urea nitrogen fell from 19 to 12 mg. per cent, and the serum potassium decreased transiently. After discontinuing the resins and supplemental salt the patient's weight increased 3 kg. in ten days despite a low salt diet; a mercurial at this time produced a weight loss of only 1 kg.

Figure 5 illustrates mobilization of severe edema by resin therapy in a seventy-two year old male patient (J. C.) who had rheumatic heart disease and diabetic intercapillary glomerulosclerosis with significant renal impair-

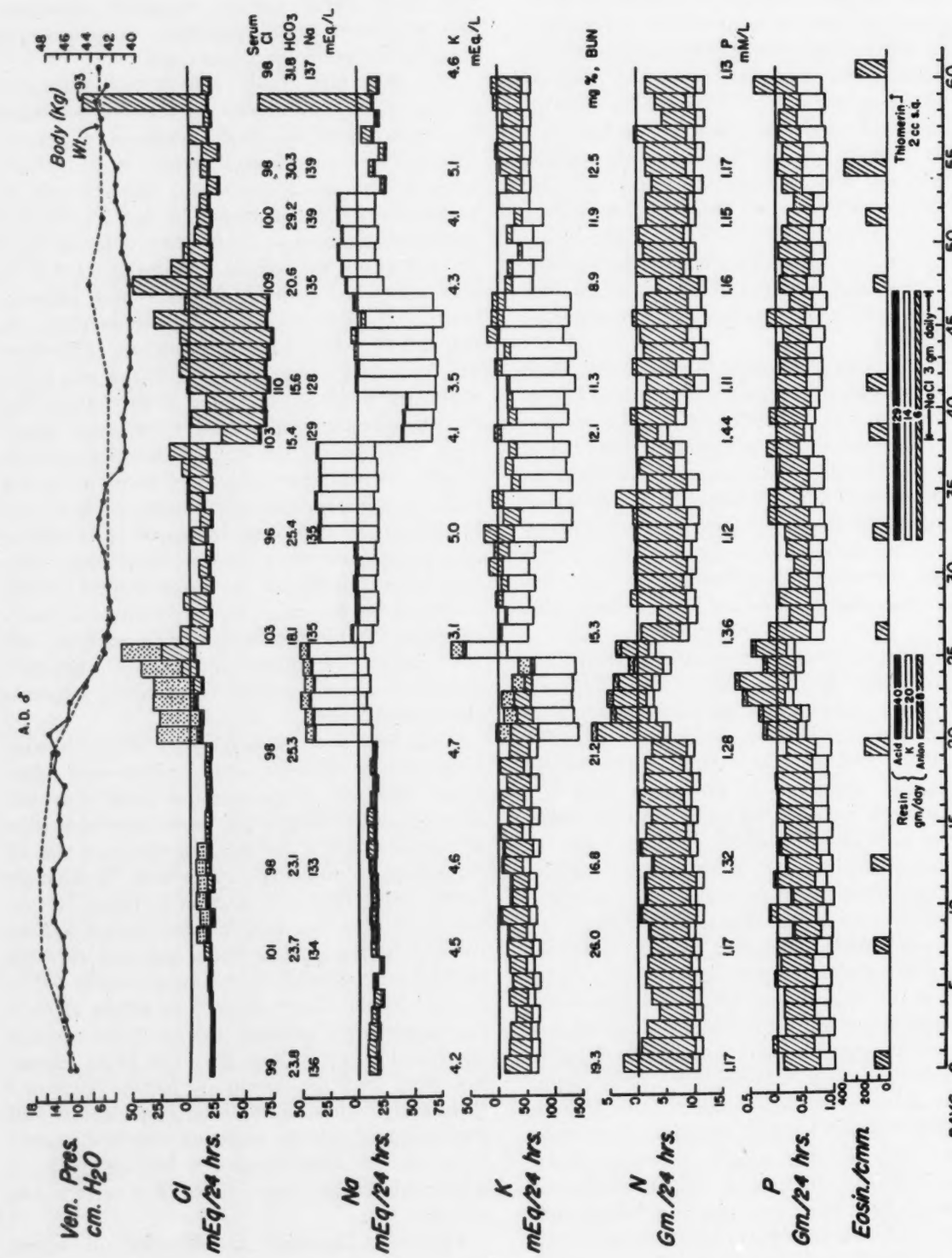

FIG. 4. Case A. D. (see text).

ment. On admission venous pressure was elevated, eosinophil count low, blood urea nitrogen 39 mg. per cent, and serum sodium, chloride, bicarbonate and potassium concentrations were 137, 105, 24 and 4.5 mEq./L., respectively. The chloruresis and natriuresis on the first charted day represent the residual effects of a mercurial diuretic given the day preceding transfer to the metabolic ward. Subsequently, he was in positive electrolyte balance prior to resin therapy.

When 40 gm. of the acid and 20 gm. of the potassium resin daily was given, a prompt increase in fecal sodium excretion and a significantly negative sodium balance occurred. Despite increased urinary potassium excretion, potassium balance remained positive but the serum potassium level was unchanged. However, urinary chloride excretion increased only slightly and severe metabolic acidosis developed. A week later, when serum bicarbonate had fallen to 13.4 mEq./L., resins had to be discontinued. The increased fecal sodium excretion

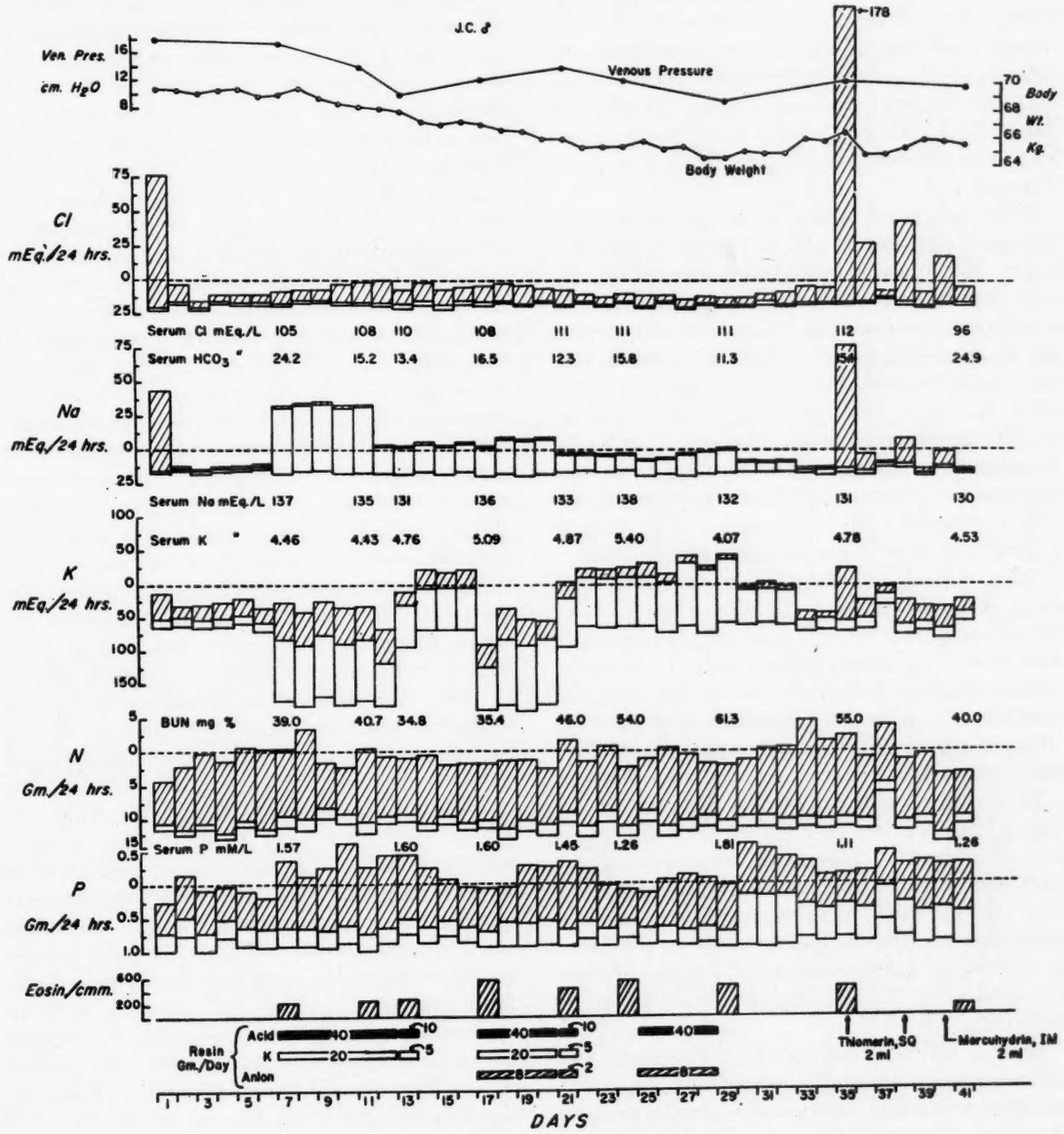

FIG. 5. Case J. C. (see text).

continued, maintaining a slightly negative sodium balance.

Three days later, when the serum bicarbonate, chloride and sodium concentrations were 16.5, 108 and 136 mEq./L., respectively, resin therapy was resumed with the addition of 8 gm. of the anion exchanger daily to the mixture. However, there were no significant changes in fecal or urinary excretion of chloride or phosphorus. As a result of the persistent, increased fecal sodium excretion without anion loss, serum bicarbonate fell to 12.3 mEq./L. with a corresponding rise in serum chloride, and resins again had to be discontinued.

Four days later, when the serum bicarbonate had risen slightly, 40 gm. of the acid resin plus 8 gm. of the anion resin were given daily for four days. There was a slight increase in stool sodium excretion during this course of the resin but no change in urinary chloride excretion and the serum bicarbonate dropped again to 11.3 mEq./L., with a fall in serum sodium but no change in chloride level. However, with the potassium-containing resin omitted from the mixture, a negative potassium balance developed with a secondary fall in the serum level, despite a marked drop in urinary potassium excretion.

After six days without resin the abnormal serum bicarbonate and chloride levels still reflected persistent severe acidosis. Therefore, a mercurial was administered with consequent profuse diuresis, leading to loss of 194 mEq. of chloride, 77 mEq. of potassium and only 92 mEq. of sodium within twenty-four hours. The increased urinary excretion of chloride and sodium continued the next day. Two days later a second mercurial was administered and there was a moderate chloruresis accompanied by increased urinary potassium excretion. Two days later a third mercurial produced only a slight chloride diuresis and virtually no natriuresis. Following the mercurials the serum chloride fell to 96 mEq./L., and the bicarbonate rose to 24.9 mEq./L.

Several times in the course of the study the patient was in markedly negative phosphorus balance, seemingly associated with the periods of acidosis. However, the variations in both fecal and urinary phosphorus excretion are difficult to interpret. The eosinophil counts of this patient at first were within normal limits, rose subsequently and fell again to the control level after the three injections of mercurials.

Figure 6 illustrates the treatment of massive edema in a fifty-six year old male patient (J. R.) with multiple myeloma and nephrotic syndrome by administration of resins and mercurial diuretics. On admission to the metabolic ward he was hyperchloremic, moderately acidotic, and had a normal serum sodium.

When given a mixture of 40 gm. of resin in the acid cycle, 20 gm. of resin in the potassium cycle and 8 gm. of the anion exchanger for six days, his stool sodium excretion increased markedly for nine days with consequent negative sodium balance and he lost 5.5 kg. After the first four days of resin therapy his serum sodium was unchanged but his bicarbonate had fallen to 14.2 mEq./L. Two days later, because his serum bicarbonate was 11.6 and chloride 118 mEq./L., resins were withheld. A mercurial diuretic was administered and the urinary excretion of chloride, sodium and potassium increased to 370, 281 and 74.6 mEq./L. respectively, in the next twenty-four hours, and remained elevated on the second day; his weight fell 3.6 kg. Despite the marked chloruresis his serum chloride level remained high and bicarbonate increased only moderately. Therefore another mercurial was administered, which was also followed by diuresis that persisted for two days. On resins plus mercurials the total weight loss was 9 kg. in twelve days. Thereafter the serum chloride, bicarbonate and sodium levels were 108, 21 and 141 mEq./L., respectively.

Then the patient was placed on the anion exchange resin alone, in daily doses of 40 gm. for two days, and 30 gm. for one day. There were no changes in urinary and stool excretion of sodium, chloride or phosphate. After the anion exchanger was discontinued, a third mercurial led to further diuresis and drop in weight. However, in the next two days, despite no additional sodium and chloride excretion, his weight continued to fall as his urine volume remained above normal, and the serum sodium level rose from 135 to 140 mEq./L. and bicarbonate from 14.0 to 17.7 mEq./L. Despite the anasarca, venous pressure in this patient was within normal limits and did not change significantly after the loss of 16 kg. of body weight.

The remainder of the chart illustrates the failure to mobilize any more fluid by the administration of salt-poor serum albumin, despite the presence of four-plus pretibial edema. Nitrogen, phosphorus and potassium balances became markedly positive during the administra-

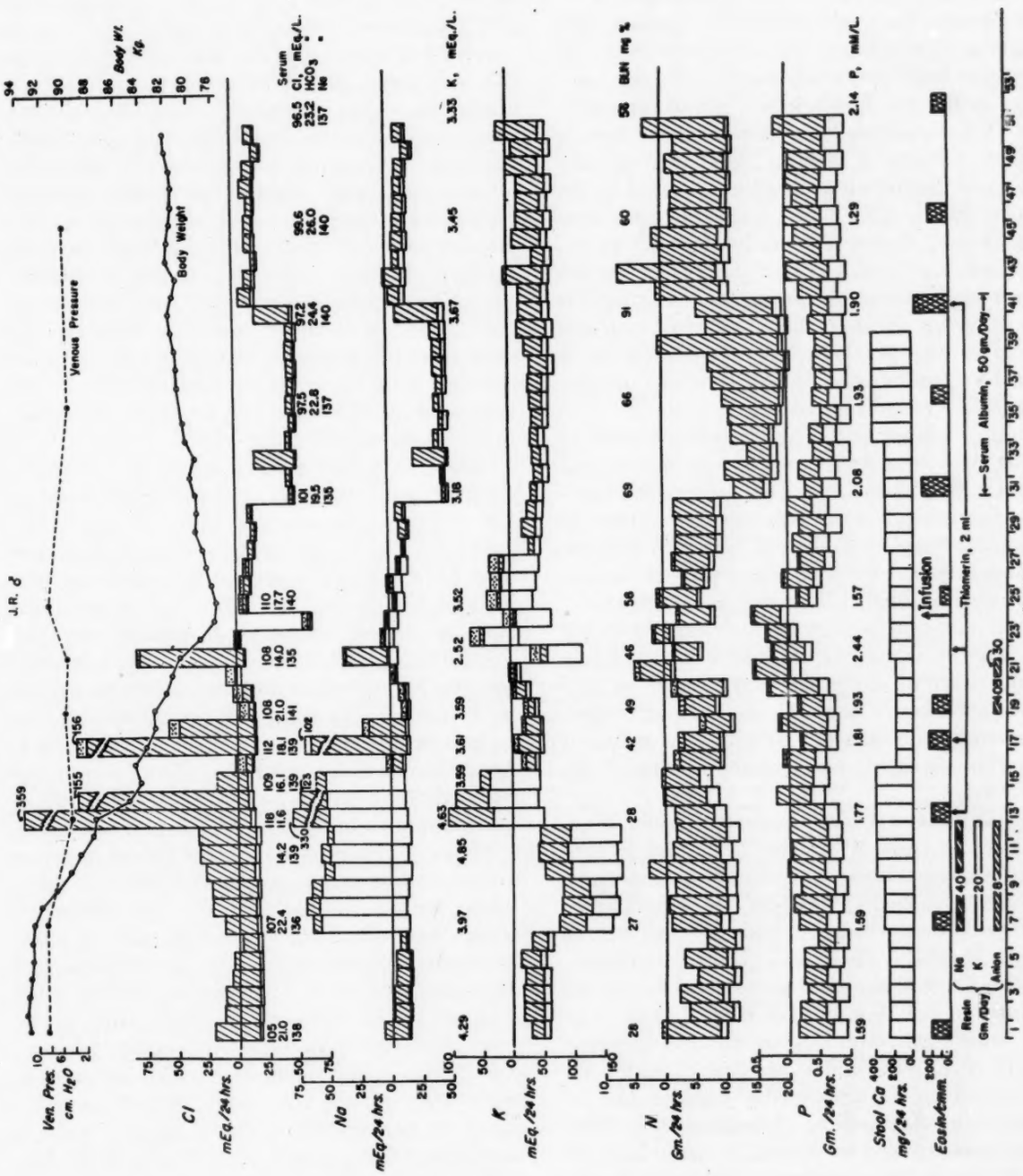

FIG. 6. Case J. R. (see text).

tion of the albumin, and stool excretion of calcium increased somewhat.

Vomiting during the seventeenth and twenty-third days resulted in a fall in serum potassium concentration and in urinary potassium excretion. From the twenty-second through the twenty-seventh day the persistent vomiting and increased fecal potassium excretion were associated with very low urinary potassium excretion. Subsequently, the patient went into a positive potassium balance, and the urinary and serum potassium gradually increased to the control levels. The blood urea nitrogen rose progressively during the study from 29 to 58, and then to 69 mg. per cent just before the infusions of the serum albumin. With administration of serum albumin the blood urea nitrogen rose to 91 mg. per cent, falling gradually to 58 after the albumin was discontinued and urinary nitrogen excretion increased.

Figure 7 illustrates the successful removal of edema fluid in a fifty-five year old woman patient (R. N.) with nephrotic syndrome of unknown etiology, who was hypersensitive to mercurial diuretics. It should be noted that the venous pressure of this massively edematous patient who, like J. R., did not have heart disease, also was within normal limits and fell only slightly when edema fluid was mobilized. At the start of the study serum sodium and potassium were normal, chloride elevated, bicarbonate decreased, blood urea nitrogen somewhat elevated, and eosinophil counts not depressed.

For four days she was placed on daily doses of 60 gm. of resin in the acid cycle and 30 gm. in the potassium cycle. Stool excretion of sodium increased markedly, leading to significantly negative sodium balance and prompt loss of weight. However, she experienced severe gastrointestinal irritation, with nausea and vomiting. Because of her severe renal disease there was little chloruresis, and her serum chloride rose to 117 mEq./L. while her bicarbonate fell to 13.4 mEq./L. despite the marked loss of chloride in the vomitus. Therefore the daily dosage was reduced to 40 gm. in the acid cycle and 20 gm. in the potassium cycle. Stool uptake of sodium decreased but sodium balance remained consistently negative. The vomiting and loss of chloride continued, and serum chloride remained about 111 mEq./L., serum sodium did not change significantly and the bicarbonate rose. In fourteen days on resin therapy there was a marked reduction in edema and a 5.8 kg. weight loss.

Forty-eight hours after resins were discontinued nausea and vomiting stopped, and her serum bicarbonate rose to 20.3, chloride was 111, and serum sodium 143 mEq./L., respectively. Six days after the first course on resin she was given 30 gm. of the acid cycle for six days. Her serum potassium, which had dropped during the previous course of resin administration due to vomiting, now fell to 2.43 mEq./L., as she went into negative potassium balance. Her stool sodium increased somewhat on this smaller dose of acid resin and her sodium balance became negative. Urinary chloride excretion increased somewhat, only little chloride being lost in the vomitus. On stopping the resin this time, however, there was a spontaneous increase in urinary sodium and chloride excretion which maintained the negative electrolyte balances for several days.

When CO_2 had again risen to 19 mEq./L., chloride was 110 mEq./L., and serum sodium 141 mEq./L., she was placed on 20 gm. of the acid resin and 10 gm. of the potassium resin per day. Fecal sodium excretion increased slightly, increased chloride excretion was maintained and the patient remained in slightly negative sodium balance. Potassium balance was markedly positive for two days and the serum potassium level rose to 3.51 mEq./L. Serum sodium, bicarbonate and chloride remained unchanged. At the time of discharge her edema was much reduced. She has been successfully maintained on intermittent resin therapy for the past two years.

Figure 8 illustrates the production of negative sodium balance in a twenty-five year old rheumatic female patient (E. W.) in congestive failure, in whom a short period of anorexia while on resins was associated with the development of potassium depletion and electrocardiographic evidence of digitalis intoxication. During the control period, although her venous pressure was at the upper limits of normal, she was in moderately severe congestive failure, as indicated by her severely reduced urinary sodium excretion. When placed on a 40 gm. daily dose of the commercial form of carbo-resin, containing 29 gm. of the cation exchanger in the acid cycle, 15 gm. in the potassium cycle, and 6 gm. of the anion exchanger for five days, she promptly developed increased fecal sodium excretion for six days. During the next three-day period there was an even greater increase in fecal

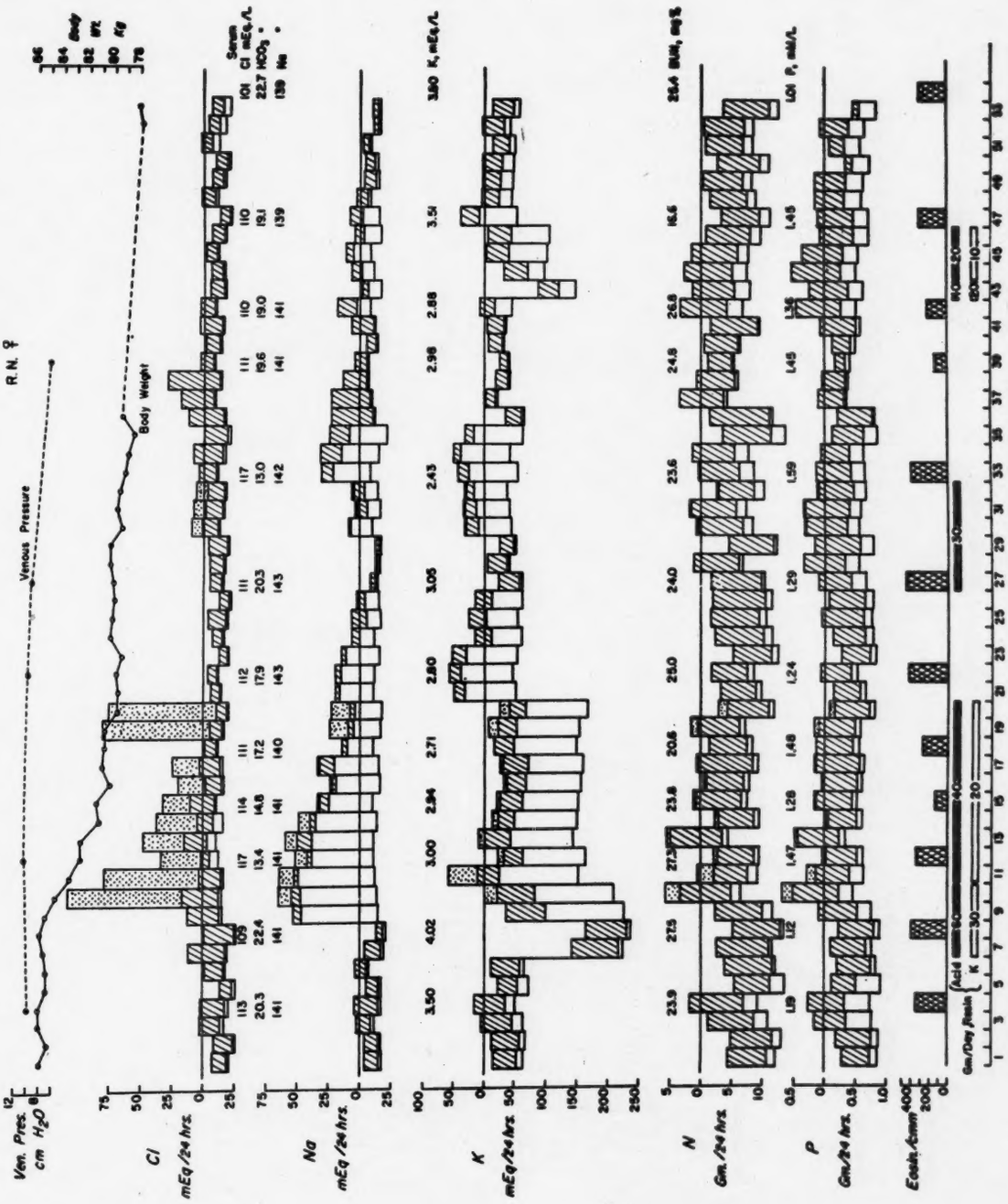

FIG. 7. Case R. N. (see text).

sodium excretion, despite her eosinopenia. With resin therapy urinary chloride excretion increased immediately and tended to compensate for the increased sodium excretion. By the fifth day, however, she developed some nausea and vomiting. The chloride lost in vomitus compensated further for the marked acidosis which she displayed that day when her serum chloride was 112 mEq./L. and her bicarbonate was 16.8 mEq./L. The day after resins were discontinued 2 ml. of a mercurial given subcutaneously led to profuse chloruresis and moderate natriuresis. There was also increased potassium diuresis which, because of her decreased food

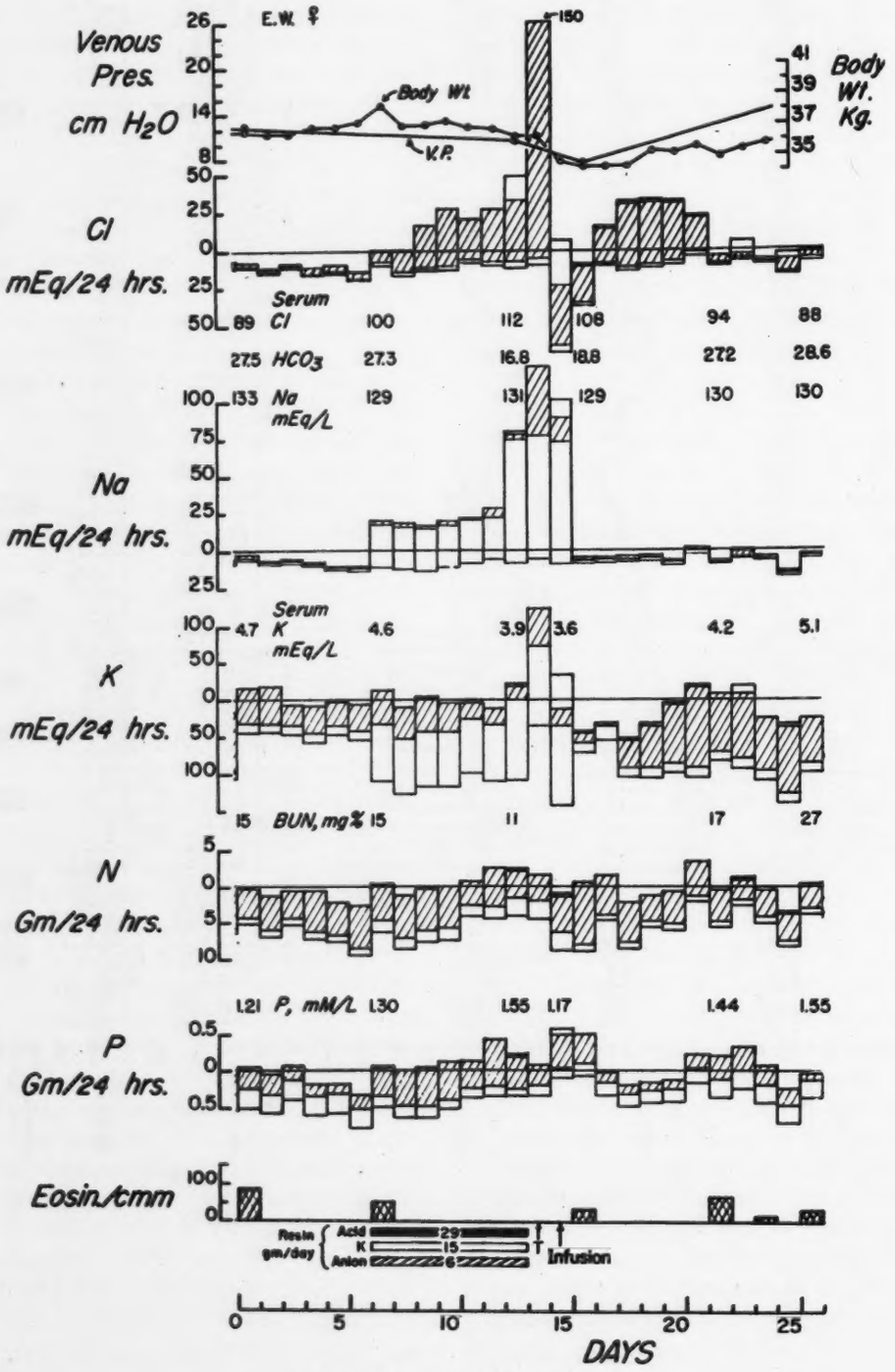

FIG. 8. Case E. W. (see text).

intake, led to a markedly negative potassium balance and a decrease in serum potassium. Electrocardiograms at this time revealed a wandering pacemaker.

Despite the profuse chloruresis, the following day her serum chloride was still high and bicarbonate correspondingly depressed. Because of continued vomiting and electrocardiographic evidence of digitalis toxicity she was given an infusion of 10 per cent dextrose in water, containing potassium chloride. Then, she was placed on oral potassium triplex® which led to positive potassium balance for four days with an increase in both serum level and urinary excretion of potassium. Following this potassium supplementation she spontaneously reverted to regular rhythm although her digitalis dosage was not reduced. In this six-day period her urinary chloride excretion continued to remain above control levels and serum chloride gradually fell to 94 mEq./L. and the bicarbonate returned to normal.

The therapeutic response achieved is reflected by the drop in body weight from 38 to 34 kg. She lost 2 kg. while on the resin, and an additional 2 kg. during the subsequent three days, which included the mercurial diuresis. Fall in venous pressure again paralleled weight loss. It should also be noted that in the period of relative potassium depletion there was a sharp drop in urinary potassium excretion which at one point was approximately 1 mEq. per twenty-four hours. In addition, this patient exhibited decreased fecal phosphate excretion during the period of resin administration, despite the presence of anion exchanger in the mixture.

COMMENTS

The present study extends the observations of others[6–13] that cation exchange resins provide a satisfactory means of mobilizing edema. Unlike previous work, however, it establishes that in edematous patients markedly negative sodium balances can be obtained by removal of large amounts of sodium from the gastrointestinal tract despite a very low sodium diet. The data also demonstrate that whether or not adrenocortical activity is increased, there may be marked resin uptake of sodium in patients with severe congestive failure on low salt diets who have eosinopenia, virtually sodium-free urines, and other evidence of intense activation of mechanisms promoting salt retention. Furthermore, in some of the patients continued resin administration did not lead to the decreased sodium uptake which has been postulated to follow compensatory decrease in the ratio of sodium to potassium concentration in the gastrointestinal tract secondary to increased adrenal cortical activity.[25,26]

Moreover, the results support the concept that cation exchange resins may be safely employed in patients with organic renal disease if certain precautions are observed. It is apparent that in renal disease, when sodium is removed by resins via the gastrointestinal tract, severe acidosis may result from accumulation of chloride which the damaged kidneys are unable to excrete. To a lesser extent there may be a similar persistence of acidosis in cardiac patients without organic renal disease, during periods when large amounts of edema fluid are being mobilized. Unpublished evidence from this laboratory suggests that the ischemic and hypoxic kidney of the cardiac may be unable to excrete chloride without sodium as rapidly as does the normal kidney during administration of resins, or of doses of ammonium chloride which produce equivalent hyperchloremic acidosis. In the cardiac the essential defect appears to be not necessarily the specific retention of chloride ion but rather an inability to provide sufficient cation in the form of ammonium ion, titratable acidity or potassium to cover an increase in urinary anion excretion. As a consequence, it is important to follow carefully the blood electrolytes of patients receiving resin therapy, even when renal disease is not clinically evident.

Whenever the serum CO_2 falls below 20 mEq./L. (45 volumes per cent), the advisability of stopping resin therapy must be seriously considered.* When serum CO_2 approaches this level administration of a mercurial diuretic, by producing a potentiated diuresis with excretion of more chloride than sodium, will tend to correct the biochemical abnormality. In patients with severe renal disease, however, administration of the mercurial may not be as effective. In these patients, or in others without known renal disease with persistent acidosis resistant to such therapy, resins may be administered

* It should be noted that resin induced acidosis, like ammonium chloride acidosis, generally is accompanied by a proportional increase in serum chloride concentration. However, in patients such as E. S. hypochloremic alkalosis, secondary to potassium depletion, may mask the degree of acidosis

safely only if given intermittently, as in patients J. C. and R. N.

As distributed for general use, carbo-resin contains an anion exchange resin in addition to the resin in the acid and potassium cycles. The anion exchange resin theoretically should increase stool excretion of phosphate and chloride, thereby tending to correct the acidosis in part. Although others have reported such increases in stool anion excretion,[9,26] our data reveal no significant change in either stool excretion of anion or in the degree of acidosis when this resin was given. Theoretically, the use of the anion exchange resin should also potentiate uptake of cation by the resin,[9] and it might be concluded that the negative sodium balances observed in these patients may have been due partly to the presence of the anion exchanger in the mixture. However, in patients S. G., E. S., M. F., R. N. and J. C., either no anion exchange resin was present in the mixture or, when it was added, no significant change in stool uptake of sodium or potassium was observed. Additional studies are required before statistically significant evidence as to the effect of the anion exchangers is available. Improvements in the anion exchanger, however, are anticipated and may contribute to the value of the resin in patients with decreased renal capacity for excreting chloride without mineral base.

Other potential complications of resin therapy —the development of hypokalemia, tissue potassium depletion without hypokalemia, or hyponatremia—may also be averted if serum electrolyte levels are periodically determined, particularly when resin therapy is first instituted. The commercially available form of carbo-resin contains sufficient potassium to avoid potassium depletion. However, in some patients in severe congestive failure, anorexia and vomiting may lead to acute potassium depletion. Consequently, if the patient's food intake is reduced, additional potassium should be provided in the form of orange juice or a mixture of organic salts.*

In the presence of gradual, resin-induced, gastrointestinal losses the kidney without organic disease may conserve potassium to a remarkable degree. For example, when patient E. S. was maintained on the acid cycle of the resin alone for a period of twelve days she lost large amounts of both sodium and potassium in her stool. Because of her normal potassium intake her urinary potassium excretion at first was 40 to 50 mEq. daily. As she continued on the acid resin there was increased fecal potassium excretion and gradual diminution in urinary potassium excretion which finally fell to less than 1 mEq./day for more than a week. At this time her serum potassium concentration was significantly reduced. Subsequently, when she was placed on a mixture of carbo-resin, containing two parts of resin in the acid cycle to one part in the potassium cycle, she went into markedly positive potassium balance. However, there was no significant augmentation of her urinary potassium excretion until her serum potassium level had risen to more than 3 mEq./L. It is of interest that at this point a mercurial diuretic, which produced profuse chloruresis, failed to increase her potassium excretion. Only when her serum potassium level rose to 4 to 4.5 mEq./L. did her urinary potassium excretion increase to control levels although the hypochloremic alkalosis, suggestive of intracellular potassium deficit, persisted.

But, as the data in M. F., J. C. and E. W. demonstrate, renal conservation of potassium alone may not suffice. Since recent studies indicate that intracellular potassium depletion may occur without significant change in serum potassium level, the other manifestations of such depletion must be kept in mind. This is particularly true in patients maintained on resins for prolonged periods of time, in whom it may occur insidiously. As mentioned above, it has been suggested that prolonged use of the resins, like the increased adrenocortical discharge associated with salt depletion[27] or severe congestive failure[25] or adrenal cortical steroid administration,[26] may lead to reduction in the ratio of sodium to potassium in the gastrointestinal secretions, thereby correspondingly altering resin uptake of these cations. Consequently, despite the potassium cycle resin in the mixture, increased resin uptake of potassium may result in depletion if anorexia decreases the patient's potassium intake. Therefore, patients should be advised to drink two to four glasses of orange juice daily while on resins, particularly if their appetites are poor, and to discontinue resins if severe vomiting or diarrhea develops.

* Oral potassium triplex,® a palatable mixture of the acetate, bicarbonate and citrate containing 15 mEq. of potassium/5 ml., supplied to us by Dr. Kenneth G. Kohlstaedt of Eli Lilly & Company, has been useful for this purpose.

If resins must be continued in the presence of anorexia, organic potassium salt mixture should be given, too. In this series although several patients had severe kidney disease, no deleterious effects of potassium administered in the resin were observed.

When serum potassium levels cannot be readily obtained, serial electrocardiograms may provide valuable information. T-wave changes may reflect the development of either hypokalemia or hyperkalemia before clinically dangerous levels are reached. The appearance of digitalis toxicity, in the presence of normal or even elevated serum potassium concentration,[28] should also lead the physician to consider the state of the patient's intracellular potassium.

A resin mixture of high potassium content permits an additional therapeutic application, as illustrated by the data and clinical course of patient S. G. When admitted to the hospital this patient had intractable edema and electrocardiographic evidence of digitalis toxicity. When carbo-resin was begun, as indicated in Figure 1, he retained much of the potassium and his potassium balance became markedly positive. As a result, it was possible to digitalize him successfully by increasing his dose of digitalis with only minimal signs of toxicity.

This observation is of importance in relation to the diuretic management of intractable edema. Ammonium chloride potentiates the response of patients resistant to mercurial diuretics. However, it produces significant increase in urinary potassium excretion, both before and after the administration of the mercurial. In a digitalized patient such loss of potassium often is accompanied by the appearance of digitalis toxicity,[28] a phenomenon erroneously attributed previously to mobilization of digitalis in the extracellular fluids. In contrast, when resin mixtures containing potassium are used in the treatment of potassium depleted cardiacs, potassium may be significantly retained, thereby permitting increased digitalis dosage, improvement of cardiac efficiency and augmented response to diuretic measures.[4]

Hyponatremia secondary to resin therapy is infrequent. Obviously, in patients with good kidney function the excretion of water and chloride in the urine should compensate for the removal of sodium from the gastrointestinal tract. However, with acute intensification of congestive failure there may be retention of water *per se*.[2] Moreover, observations in this and other laboratories indicate that there may be significant continued retention of water in excess of sodium in patients in chronic congestive failure.[1,2] In this situation removal of sodium from the gastrointestinal tract may not be accompanied by a commensurate increase in excretion of water by the kidney. Consequently, there conceivably may be a decrease in the serum sodium concentration unless this is maintained by withdrawal of sodium from other body stores.[29] Therefore, before or during the administration of resins any mechanisms promoting primary water retention should, if possible, be eliminated.

Other factors may tend to lower serum sodium concentration in patients on resin therapy. One may be a shift of sodium from the extracellular compartment into either cells or other extracellular areas like bone. For example, in patients S. G. and E. S. the weight loss during resin therapy was considerably greater than could be explained by the change in external sodium balance, as others have reported.[12] Despite this there was continued decrease in the concentration of sodium in the extracellular fluid with resin therapy as the usual hyperchloremic acidosis developed. One explanation may be that electrolyte transfer from the extracellular fluid into some non-extracellular compartment may have produced a drop in the extracellular sodium. As a result there may have been further inhibition of posterior pituitary secretion of antidiuretic hormone, leading to increased urine flow and additional reduction in extracellular volume. The lowered serum sodium concentration observed under these circumstances, therefore, could reflect some residual effect of this electrolyte shift.

Precisely what physiologic change might have stimulated such a transfer of sodium is difficult to determine. It is tempting to ascribe both this shift of sodium and the water diuresis to the development of hyperchloremic acidosis. However, we have not observed significant water diuresis or decrease in serum sodium concentration in other edematous cardiac patients in whom a comparable degree of hyperchloremic acidosis had been produced by administration of ammonium chloride.[30] Unfortunately, in the latter group the acidosis, although equivalent in degree, was not as prolonged as that occurring in cardiac patients receiving resins.

While the postulated shifts may have contributed to the transient hyponatremia observed in M. F., A. D. and J. C., it should be emphasized that the occurrence of such hyponatremia is unusual. For example, patient J. R., with severe renal disease, showed little change in serum sodium concentration while on resin therapy, and patient R. N., who also had renal disease, exhibited none. However, the latter, although well controlled on resin therapy, at times vomited profusely, losing large amounts of chloride, which tended to prevent the development of severe acidosis.

Thus clinically significant hyponatremia should rarely occur in any patient receiving resins if periodic checks of serum electrolyte concentrations are made. Furthermore, it will be even less likely to occur if, once edema has been mobilized, the dose of resin is reduced in proportion to the salt intake, or the salt intake is somewhat increased, since resin uptake of sodium sometimes may not decrease with continued use.

Considering the available facts, it would appear that sodium-removing resins provide a valuable addition to the therapy of edema. In edematous cardiac and renal patients previously resistant to almost any form of therapy there may not only be successful mobilization of edema fluid but also partial correction of severe potassium depletion, permitting adequate digitalization and improvement in the cardiac status.

For such clinical application, however, certain principles should be borne in mind. First, there should be periodic determination of the serum electrolyte concentrations, particularly whenever vomiting, diarrhea or any acute exacerbation of the underlying congestive failure is present. If the serum bicarbonate level falls below 20 mEq./L., with a corresponding rise in the serum chloride concentration, discontinuance of resin therapy should be seriously considered. Administering a mercurial diuretic to promote the excretion of chloride may help to correct the hyperchloremia. Generally, as a result of the hyperchloremic acidosis a potentiated effect of mercurial diuretics is observed in most patients.[13] In cardiacs, once resins have begun to mobilize edema, thereby interrupting the vicious cycle of congestive failure, even greater diuresis after mercurials than can be explained on the basis of the acidosis alone may occur as the intensity of failure diminishes.[4] In edematous patients with renal disease, resin therapy, if used carefully and intermittently, may be employed with little danger.

Second, if the principles outlined above are followed, other biochemical abnormalities such as potassium depletion with or without hypochloremic alkalosis or hypokalemia, and the rarer hyponatremia, may be averted. As in the case of any other potent therapeutic agent, the patient should be instructed to discontinue therapy and consult his physician whenever any untoward symptoms are noted.

Third, the dose of resin, the time of administration, the vehicle in which it is prepared, and the clinical response all must be carefully established for each patient. The degree of success in applying resin therapy will depend upon both the physician and the patient. For example, some patients may develop abdominal distress, nausea, vomiting, diarrhea or constipation while on resin therapy. However, as in this series, encouragement by the physician, variation of the resin schedule, application of the usual therapeutic methods, and the cooperation of a sufficiently motivated patient can do much to overcome these gastrointestinal symptoms.

Generally, in those edematous patients who can successfully complete the early period of adjustment to resins, mobilization of edema often previously resistant to other therapy may be accomplished and a relatively edema-free state maintained even on an increased sodium intake. Properly used, sodium-removing resins have an important place in the management of patients with edema difficult to control by the usual means. In any patient, only a therapeutic trial can determine whether these agents will be effective.

SUMMARY

The effects of ion exchange resins on the metabolic balances of sodium, chloride, potassium, nitrogen and phosphorus were studied in eleven edematous patients with either cardiac or renal disease.

Administration of 40 to 90 gm. daily of a carboxylic acid cation exchanger, two-thirds in the acid cycle and one-third in the potassium cycle, produced marked increases in fecal sodium excretion, significantly negative sodium balances, and effective loss of edema. These effects were observed even in patients in severe congestive failure on low sodium diets who exhibited evidence of actively functioning

sodium-conserving mechanisms, such as negligible urinary sodium excretion and eosinopenia.

As a result of removal of cation without anion, persistent hyperchloremic acidosis developed, despite the increased urinary chloride excretion and the negative chloride balance which promptly occurred in patients without organic renal disease. In patients with renal disease little chloruresis occurred and, consequently, the resulting acidosis was more severe. However, by intermittent administration of the resins and the concurrent use of mercurial diuretics, which produced loss of more chloride than sodium, mobilization of edema in the patients with renal disease was safely accomplished.

In this series, addition of an anion exchanger to the resin mixture had no effect on either the acidosis or the fecal excretion of any electrolyte. The proportion of resins in the potassium cycle in carbo-resin provided sufficient additional potassium, as a rule, to prevent potassium depletion. Moreover, with gradual, resin-in-induced gastrointestinal losses, the kidney very efficiently conserved potassium by reducing the urinary excretion to less than 1 mEq./day. However, when patients on resin therapy developed anorexia and vomiting or diarrhea, the additional loss of potassium tended to produce depletion with or without hypokalemia. If signs of potassium deficit occur, oral supplementation of the patient's intake with organic potassium salt mixtures permits continued resin therapy.

Hyponatremia is a rare consequence of resin therapy. Since there is generally greater diuresis and weight loss than can be explained on the basis of the increased sodium excreted, this cannot represent sodium depletion *per se*. Whether movement of sodium into some non-extracellular site may be involved in the transient, spontaneously reversible, mild hyponatremia observed in some cardiacs during the period of hyperchloremic acidosis of resin therapy remains to be established.

It is concluded that, if periodic blood studies are made throughout therapy, the administration of resins constitutes a valuable and safe addition to the treatment of resistant edema in patients with cardiac and renal disease. The value of these agents in any individual patient must be determined empirically.

Acknowledgments: We are grateful to Miss Hilda Fisher, Mrs. Maidie Ross, Mrs. Anna Cohen, Mrs. Hattie L. Heavner and Mr. George Ross of our laboratories, and to Miss Anne Goehring, Miss Eunice E. Hering and Miss Tinnie L. Bonner, nurses on our Metabolic Ward, for their valuable assistance.

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Treatment of Edema by Removal of Body Sodium by a Cation Exchange Resin*

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WHEN cation exchange resins were first introduced for the treatment of edematous patients, it was hoped that they would remove clinically significant quantities of sodium in the feces of patients receiving low sodium diets. However, the reported experience on this aspect of resin therapy has been disappointing.[1,2] In a recent appraisal of the clinical value of cation exchange resins Danowski[3] concluded that they are of value in preventing sodium absorption by patients on moderate sodium intakes but will not remove sodium from the edema fluid of patients on low sodium diets.

The results reported in the present paper are not in accord with that conclusion. The removal by a cation exchange resin of clinically significant quantities of sodium from the edema fluid of patients on low sodium diets is described.

The pharmaceutical preparation used was resodec®† which is prepared from amberlite XE-96,® a carboxylic cation exchange resin. Amberlite XE-96 is a pharmaceutical grade of amberlite IRC-50,® a cross-linked, polyacrylic polymer with a cation exchange capacity of 10 mEq. per gm. of hydrogen form resin. Its exchange characteristics have been described by Kunin and Barry.[4] Resodec is a mixture of the ammonium and potassium forms of XE-96 containing 1.6 mEq. of potassium per 10 mEq. of resin (1.3 mEq. per gm. of resin). It is a fine, white powder (100 to 200 mesh in size) and contains a flavoring agent and an agent to aid in its suspension in water.[5]

CHEMICAL METHODS

The resin and potassium content of resodec, and the resin, sodium and potassium content of feces were measured by the following modification of a method described by Heming.[5]

The feces are homogenized with water, and an aliquot containing approximately 5 mEq. of resin is stirred fifteen minutes with 40 ml. of normal HCl. The supernatant is separated by centrifugation and the residue washed four times with 30 ml. of water. The combined supernatant and washings are analyzed for sodium and potassium, and the quantities of these cations in the feces calculated. The residue, containing the resin now in the hydrogen form, is stirred thirty minutes with 40 ml. of normal NaOH. The supernatant is discarded and the residue washed six times with 30 ml. of water. The residue, containing resin now in the sodium form, is stirred fifteen minutes with 40 ml. of normal HCl. The supernatant is separated and the residue washed four times with 30 ml. of water. The sodium content of the combined supernatant and washings is determined. Since this quantity of sodium equals the resin present in the aliquot, the amount of resin present in the feces can be calculated. Analysis of feces containing no resin gives an apparent value of about 4 mEq. of resin per day. Resin added to feces can be quantitatively recovered.

Sodium and potassium were determined with an internal standard flame photometer,[6] urinary and serum chloride by the method of Sendroy as modified by Van Slyke and Hiller[7] and dietary chloride as described by Van Slyke.[8] The digestion procedure of Wallace and co-workers[9] was used for dietary sodium and potassium.

SUBJECTS

Four patients with moderate to large amounts of edema fluid were studied. W. L. and N. M.

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† Resodec was supplied through the courtesy of Mr. Michael Buckley of Smith, Kline and French Laboratories.

had heart disease with congestive failure. W. P. and E. G. had intercapillary glomerulosclerosis. Both renal and cardiac disease were considered important in the origin of their edema. Protocols of the patients are given in detail below.

W. L., a sixty-one year old man, first noted edema and dyspnea four years before the present admission. He was treated with digitalis, salt restriction and mercurial diuretics both as an outpatient and during several hospital admissions prior to the present admission. On examination venous distention, cardiac enlargement, a totally irregular cardiac rhythm, hepatomegaly, ascites and severe edema were apparent. Blood pressure was normal. Electrocardiogram showed auricular fibrillation and left axis deviation. Teleroentgenogram showed marked cardiac enlargement. The results of hematologic studies and urinalysis were normal. He was treated with digitoxin, sodium restriction, frequent injections of a mercurial diuretic and abdominal paracentesis. After an initial diuresis with a loss of 27 kg. he ceased to lose weight on this regimen. At this time marked edema persisted and his venous pressure was 16 cm. of water. Treatment with resin was started. The patient was thought to have arteriosclerotic heart disease with congestive failure.

N. M., a forty-five year old woman, had been known to have hypertension for twenty years. Eighteen years before the present admission she was treated for syphilis. Dyspnea and edema developed four years before the present admission. She was treated with digitalis, salt restriction and mercurial diuretics both as an outpatient and during several hospital admissions prior to the present admission. At the time of admission, examination revealed marked venous distention, numerous basilar rales, marked cardiac enlargement and aortic diastolic and systolic murmurs. Blood pressure was 220/110. Hepatomegaly and dependent edema were present. Electrocardiogram showed left axis deviation. Teleroentgenogram revealed aortic dilatation and marked cardiac enlargement. The results of urinalysis and hematologic studies were not noteworthy. Serologic test for syphilis was positive. Digitalis and sodium restriction were continued. On the first hospital day she received 2 cc. of mercuhydrin. This was followed by a weight loss of 2.7 kg. On the second hospital day she was started on the constant diet which she received throughout the subsequent balance study. Because of the severity of her dyspnea it was not advisable to carry out a control period prior to the administration of resin. However, since she was nauseated and vomited several times daily, the possibility existed that resin might increase her nausea. She was therefore given only 120 mEq. of resin per day on the second and third hospital days. Vomiting ceased and on the fourth hospital day the balance study during which she received 360 mEq. of resin per day was started. Her weight remained constant during the two days that she received 120 mEq. of resin per day, showing that she was not diuresing prior to the administration of the larger dose of resin. Analyses of urine and feces were not made on the two days that she received the smaller dose of resin. This patient was thought to have hypertensive cardiovascular disease and slight syphilitic aortic insufficiency with congestive failure.

W. P., a fifty-nine year old man, was found to have diabetes mellitus eight years before the present admission. He did not take insulin regularly but remained asymptomatic until one month before admission when edema of the legs appeared. There was no past history suggestive of renal disease. Blood pressure was 190/100. Moderate venous distention was present. Cardiac sounds were normal. The liver edge descended 1 cm. below the costal margin. There was moderate edema of the lower extremities up to the sacrum. Electrocardiogram showed left axis deviation. Teleroentgenogram showed that the heart was enlarged. Urinary sediment contained a few erythrocytes, leukocytes and granular casts per high power field. Urinary protein was about 13 gm. per day. Hematocrit was 39 per cent, fasting blood sugar 159 mg. per 100 cc. and blood urea nitrogen 18 mg. per 100 cc. Serum albumin was 2.3 and globulin 2.1 gm. per 100 cc. There was 30 per cent excretion of phenolsulfonphthalein in the first fifteen minutes after intravenous injection of the dye. Urea clearance was 48 per cent of normal. The patient was not digitalized. On the third hospital day he was started on the balance study. He was thought to have intercapillary glomerulosclerosis with renal damage and hypertensive cardiovascular disease. The edema was attributed to the nephrotic syndrome and congestive failure.

E. G., a forty-eight year old man, had been known to have diabetes mellitus for twelve years. Hyperglycemia had been adequately controlled with diet and 20 units of protamine

zinc insulin daily. Fifteen months before the present admission dependent edema appeared and six months later dyspnea developed. He was treated with digitalis and salt restriction both as an outpatient and during several hospital admissions prior to the present admission. At the time of the present admission, examination revealed retinal arterial narrowing, hemorrhages and exudates. Basilar rales were present. Blood pressure was 180/100. Cardiac sounds were normal. The liver edge was felt 2 cm. below the costal margin. There was moderately severe edema of the lower extremities up to the sacrum. Electrocardiogram showed evidence of left ventricular strain, and teleroentgenogram showed cardiac enlargement. Urinary sediment contained a few erythrocytes, leukocytes and granular casts per high power field. There was about 12 gm. of urinary protein per day. Hematocrit was 29 per cent, fasting blood sugar was normal and blood urea nitrogen was 38 mg. per 100 cc. Serum albumin was 1.6 and globulin 2.4 gm. per 100 cc. There was 15 per cent excretion of phenolsulfonphthalein in the first hour after the intravenous injection of the dye, and urea clearance was 24 per cent of normal. Digitalis and salt restriction were continued. Prior to the balance study the patient was slowly diuresing. He continued to diurese at the same rate during the control period of the balance study. The patient was thought to have intercapillary glomerulosclerosis with renal damage and hypertensive cardiovascular disease. The edema was attributed to the nephrotic syndrome and congestive failure.

EXPERIMENTAL PROCEDURE

In the cases of W. L., W. P. and E. G. there were control periods six to seven days in length. Because of the severity of N. M.'s pulmonary edema there was no formal control period. However, the first two days of resin therapy, during which she received only 120 mEq. of resin per day, serve as a control period in that the absence of weight loss in that period indicates that she was not diuresing prior to the administration of the larger amount of resin. Analyses of urine and feces were not made on those two days. The periods of resin therapy in the four cases lasted from thirteen to forty-six days.

Each patient received a constant weighed diet. N. M. was unable to eat consistently all the food offered her. Thus information about her intake is limited to the knowledge that it was usually less than that offered. Throughout most of the study the diet of W. L. contained 42 mEq. of sodium, 86 mEq. of potassium and 34 mEq. of chloride per day. In the last six days of the study the intakes were increased to 49 mEq. of sodium, 107 mEq. of potassium and 37 mEq. of chloride per day. The diet for N. M. contained 16 mEq. of sodium, 91 mEq. of potassium and 16 mEq. of chloride; that of W. P. 19 mEq. of sodium, 114 mEq. of potassium and 24 mEq. of chloride; and that of E. G. 17 mEq. of sodium, 112 mEq. of potassium and 24 mEq. of chloride per day. The resin added 53 mEq. of potassium per day to the diet of W. L. and 58 mEq. per day to each of the other diets.

The patients were ambulatory. No therapeutic measures other than digitalis and resin were employed during the study. The patients on digitalis had received that drug for periods of months or years prior to resin therapy. W. L. was usually constipated and was given 8 cc. of fluid extract of aromatic cascara daily in both control and resin periods. While on this medication he usually had one semiformed stool per day. Because it was anticipated that laxatives might be given during the period of administration of resin, E. G. and W. P. received 4 to 6 cc. of cascara on three days of their control periods. This caused a mild diarrhea in these patients. However, neither they nor N. M. were given laxatives during the periods of resin therapy.

Throughout the studies body weight, fecal excretions of sodium, potassium and resin, and urinary excretions of sodium, potassium and chloride were measured. Serum sodium, potassium and CO_2 combining power were determined frequently. Urinary and fecal determinations were made on the combined collections of periods three to seven days in length. The stools were assigned to the days on which they were passed except in the case of W. L. in which fecal periods were demarcated with carmine.

In the case of W. L. resin dosage was 330 mEq. per day (41 gm. per day), and in the other three cases 360 mEq. per day (45 gm. per day). The resin was taken between meals in three equal doses. The milliequivalents of resin per gm. of resodec were determined analytically and the resin weighed out in the desired dosage.*

* There are about 8 mEq. of resin per gm. of resodec. This figure is less than the capacity of the hydrogen form largely because of the greater weight of the ammonium and potassium ions.

RESULTS

The data are presented in Figures 1 through 4 and in Table 1.

Clinical Data. The control period established that W. L. was not diuresing. Resin therapy resulted in diuresis with a total weight loss of

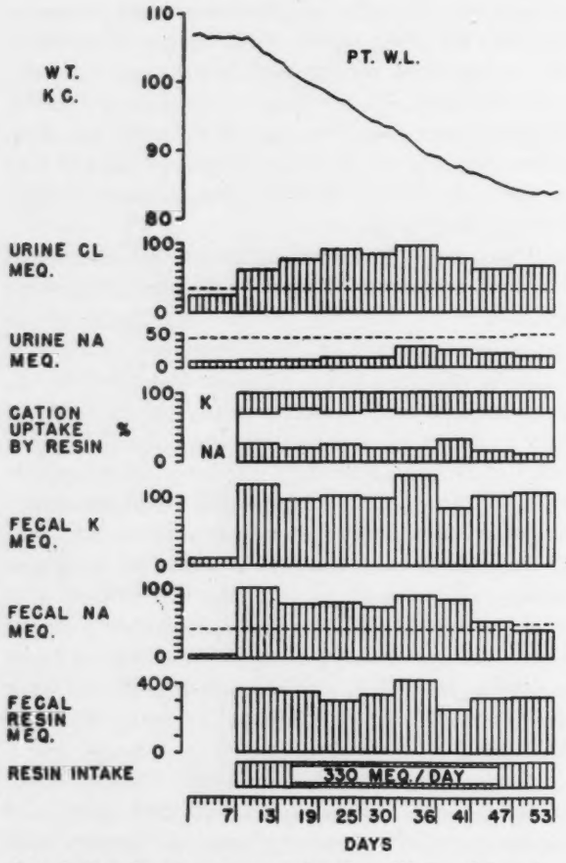

FIG. 1. Results of treatment of patient W. L. with resin. In this and the subsequent figures the average daily data are plotted. The dotted lines represent the daily intakes of sodium and chloride. The per cent uptakes of sodium and potassium are the mEq. of sodium and the mEq. of potassium per 100 mEq. of resin.

22.2 kg. and apparently complete disappearance of edema. In the case of N. M. there was no weight loss during the two days when resin dosage was only 120 mEq. per day. When the dosage was increased to 360 mEq. per day, diuresis occurred, resulting in the loss of 16.6 kg. and complete disappearance of edema. W. P. was diuresing during the control period. During the administration of resin the rate of diuresis increased. Total weight loss was 8.9 kg. and only a trace of pretibial edema remained at the end of the period of study. E. G. was diuresing slowly at the time resin therapy was started. Resin therapy had little effect on the diuresis. Moderate edema remained at the end of the period of treatment with resin. Thus resin therapy in two cases initiated diuresis, in one case accelerated an existing diuresis and in one case had little effect on diuresis.

TABLE 1
SERUM ELECTROLYTE CONCENTRATIONS*

Case		Days of Administration of Resin†							
		1	7	13	19	25	31	37	47
W. L.	Na	136	141	138	136	138	137	139	142
	CO_2	26	23	20	24	19	24	25	27
	K	4.3	4.1	4.0	3.9	4.1	3.8	3.8	3.4
N. M.	Na	131	128	133	133	130	129		
	CO_2	25	16	22	20		20		
	K	4.6	5.2	5.0	4.9	5.0	4.6		
W. P.	Na	144	143	143	141				
	CO_2	29	18	23	22				
	K	5.4	5.3	5.3	5.1				
E. G.	Na	143	143	144					
	CO_2	21	14	12					
	K	6.1	5.2	4.8					

* Sodium, potassium and CO_2 combining power are expressed as mEq./L.

† Blood was drawn before medication for day; value on day one is thus a control value.

No symptomatic manifestations of undesirable effects from resin were apparent. The rather severe acidosis which developed in E. G. was asymptomatic.

Fecal Data. During the entire period of the study W. L. excreted 99 per cent, N. M. 89 per cent, W. P. 49 per cent and E. G. 38 per cent of the ingested resin.

Early during the administration of resin the fecal excretion of sodium greatly exceeded dietary intake in the cases of W. L., N. M. and W. P. but not in the case of E. G. In the three cases in which fecal excretion of sodium was large during resin therapy, the uptake of sodium by resin varied initially from 25 to 30 per cent

of the total exchange capacity of the resin.* As edema cleared uptakes fell to a range of 5 to 20 per cent. In the case of E. G., in which resin was relatively ineffectual, the average uptake was only 5 per cent.

In the three cases with high sodium uptakes

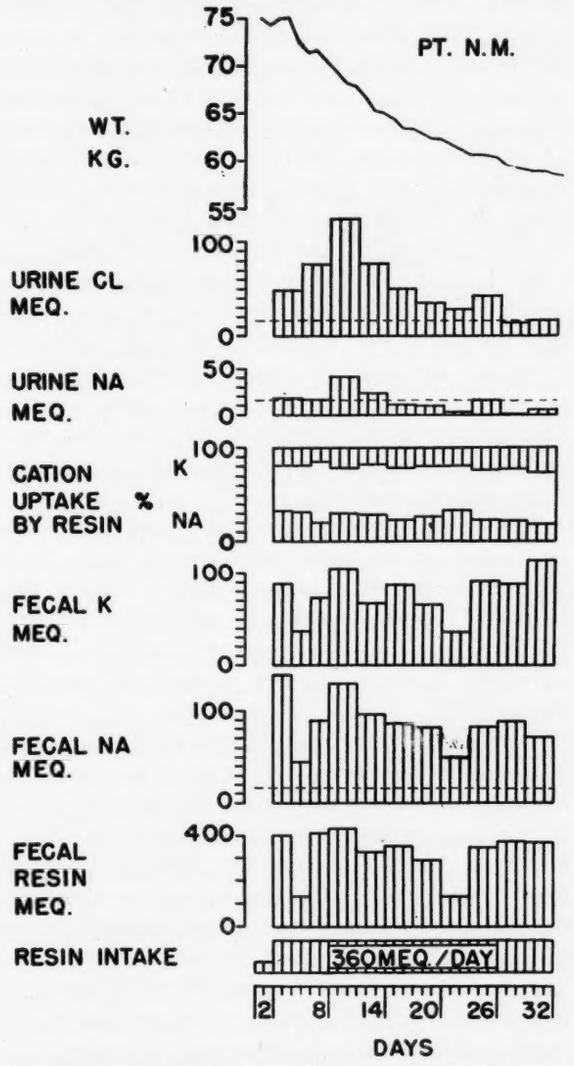

FIG. 2. Results of treatment of patient N. M. with resin. The patient was usually not able to eat the entire diet, therefore sodium and chloride intakes were less than indicated by the dotted lines.

the uptakes of potassium by resin varied from 14 to 30 per cent while sodium uptakes were high. When sodium uptakes fell, the uptakes of potassium by resin rose in the cases of N. M. and W. P. In the case in which sodium uptake was small potassium uptake was as high as 47 per cent.

The sum of sodium and potassium uptakes

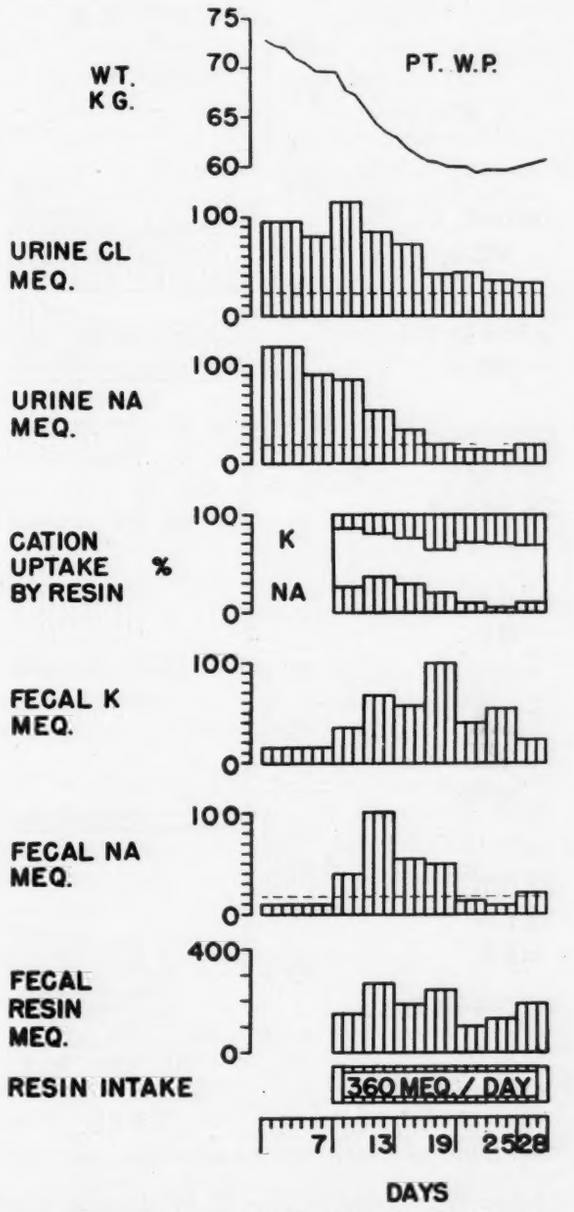

FIG. 3. Results of treatment of patient W. P. with resin.

was relatively constant. The mean uptake of sodium plus potassium for all patients was 48 per cent of the total capacity of the resin.

Urinary Data. Urinary sodium excretion did not follow a uniform pattern. During resin therapy it increased slightly in the cases of W. L. and E. G., and decreased in the case of W. P.

* The uptake of sodium or potassium by resin is expressed as the per cent of the total exchange capacity of the resin in the sodium or potassium form. Five mEq. of fecal sodium and 10 mEq. of fecal potassium per day were assumed to be not combined with resin. The rather high figure for fecal sodium was chosen to be sure that sodium uptake was not overestimated. A sodium uptake by resin of 25 per cent is the same as an uptake of 2 mEq. of sodium per gm. of resodec.

It was low throughout the period of therapy in the case of N. M.

Urinary excretion of potassium decreased during the administration of resin. In the control periods the average daily urinary potassium excretions in milliequivalents were 71 for W. L.,

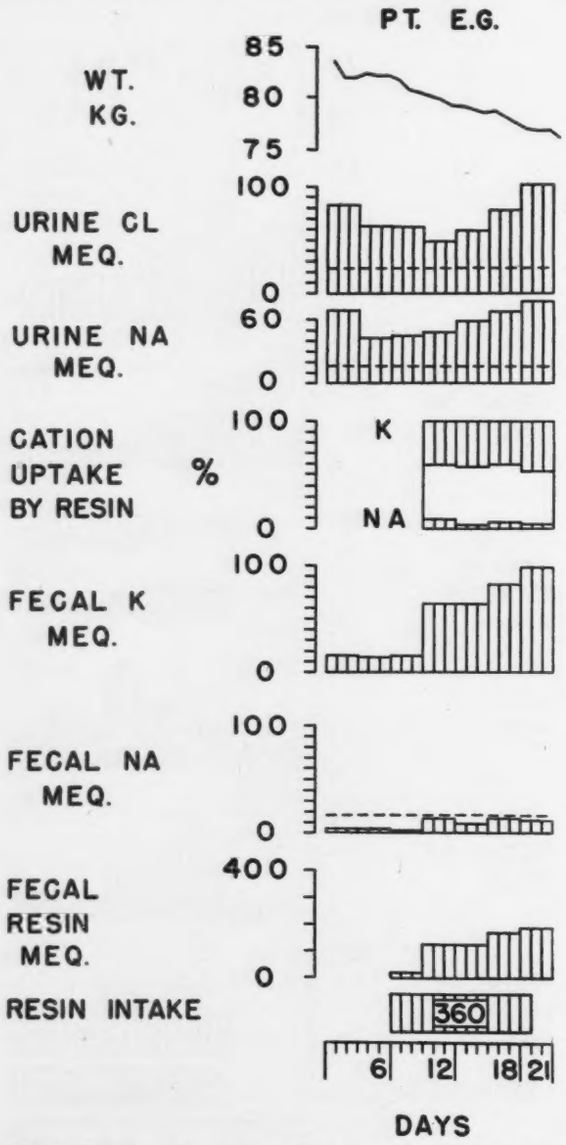

FIG. 4. Results of treatment of patient E. G. with resin.

55 for W. P. and 50 for E. G. During resin therapy the average daily urinary potassium excretions in milliequivalents were 49 for W. L., 40 for W. P., 27 for E. G. and 24 for N. M.

In the three cases in which large quantities of sodium were excreted in the feces, urinary chloride excretions were large. In the case in which small quantities of sodium were excreted in the feces urinary chloride excretion was moderately increased over that of the control period.

Balance Data. Computation of balances for sodium and potassium in this study is subject to the limitation that the resin remaining in the intestinal tract at the completion of the study was combined with unknown quantities of these cations. Therefore balances computed as the difference between dietary intake and fecal and urinary excretion are referred to as apparent balances. The total apparent negative balances for sodium for the entire period of study after initiation of resin therapy were for W. L. 2,316 mEq., for N. M. greater than 2,564 mEq., for W. P., 1,185 mEq. and for E. G. 789 mEq.

W. L. had a negative balance for potassium which was not greater than the error of the balance study. W. P. and E. G. had sufficient retention of resin to render their apparent positive balances of potassium meaningless. The balance in the case of N. M. was not computed since the uncertainty as to dietary intake of potassium was too great.

The total calculated negative chloride balances during the administration of resin were 2,017 mEq. for W. L., more than 873 mEq. for N. M., 777 mEq. for W. P. and 609 mEq. for E. G. These balances were computed as the difference between dietary intake and urinary output.

Serum Data. Serum sodium concentrations did not change significantly in any of the patients during the administration of resin. Serum potassium concentrations decreased slightly in W. L. and E. G. but not in the other subjects. In three cases CO_2 combining power fell moderately during resin therapy and then returned to or toward the control values. In the case of E. G., who had severe renal disease, the CO_2 combining power declined markedly and remained low during resin therapy. (Table 1.)

COMMENTS

The experience so far reported in the literature[1,2] is that cation exchange resins will not remove clinically significant quantities of sodium from edema fluid by withdrawing sodium in the feces in excess of dietary intake. Their therapeutic value in the treatment of edema has been thought to lie primarily in their ability to decrease sodium absorption on higher sodium intakes.[3]

However, it is apparent from the results obtained in the present study that the cation

exchange resin employed can remove large quantities of sodium in the feces of some edematous patients receiving low sodium diets. Since fecal sodium excretion may greatly exceed dietary intake, the excess must be body sodium which has entered the intestinal tract in the various gastrointestinal secretions.

The difference between the results of this study and previous studies probably can be explained on the basis of differences in patients and differences in the quantity of edema present at the time the resin was administered. Even in those cases in the present study in which resin therapy was highly effective, relatively poor uptakes of sodium by resin were obtained after the patients became essentially free of edema. The difference between the results of this study and the results of previous studies is not due to the resin employed since pharmaceutical grades of amberlite IRC-50 have been previously used.[1,2]

The cause of the poor uptake of sodium by resin in some edematous patients and the fall in uptake in other patients as their edema clears is unknown. Berger and co-workers[10] have shown that desoxycorticosterone acetate will decrease the uptake of sodium by resin. Probably hormonal factors play a role in the low uptakes that are observed in some patients initially and in others after edema has cleared.

As a result of the removal of body sodium on the resin there is increased urinary excretion of water and chloride in such amounts that the composition of extracellular fluid is only moderately disturbed while its volume is reduced to a normal value. However, if renal function is inadequate to effect this adjustment of extracellular fluid composition, severe acidosis may result.

In the present study the uptake of potassium by excreted resin was usually greater than the amount of potassium supplied by the ingested resin. The amount of potassium absorbed from the intestinal tract was therefore reduced. Because of reduced renal excretion of potassium significant potassium depletion did not occur. However, it may occur if resin is given anorexic patients whose dietary intake of potassium is low. In several such patients mild potassium depletion has been observed.[11] Potassium depletion is also more liable to occur when uptake of sodium by resin is low since low uptakes of sodium are associated with high uptakes of potassium.

The very slow elimination of ingested resin in some patients indicates that this material may move at a much slower rate than is ordinarily attributed to food residues. No adverse effects of this slow excretion of resin were observed.

It is apparent that the cation exchange resin employed in this study is a useful therapeutic agent in the treatment of edema. Clinically significant acidosis and potassium depletion are not likely to occur in properly selected patients. If the latter appears possible because of poor dietary intake, supplementary potassium salts can be given. The resin may be used advantageously in combination with mercurial diuretics which it potentiates.[12]

CONCLUSIONS

Amberlite XE-96, a carboxylic cation exchange resin, is an effective agent in the treatment of edema.

This resin will remove body sodium in the feces of edematous patients receiving low sodium diets. As edema clears, progressively less sodium is removed by the resin.

If renal function is adequate, clinically significant acidosis does not occur. In the presence of sufficiently severe renal disease marked acidosis may develop.

If the resin ingested is partially in the potassium form and dietary intake is adequate, potassium depletion is unlikely to occur.

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Heparin Treatment of Angina Pectoris*

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IN 1943 Hahn[6] made the observation that intravenous injection of heparin increases the translucency of plasma during alimentary lipemia. By means of nephelometry and chylomicron counting, subsequent investigators[1,2,7] could confirm this action of heparin on the lipoid particles of the plasma. The possibility that the heparin effect is due to formation of strongly surface active heparin-phospholipid complexes was rendered probable by the investigations of Anderson and Fawcett.[1]

By means of ultracentrifugation Gofman and co-workers[3,4] could demonstrate lipoprotein particles of varying orders of magnitude in plasma; as is well known, they attribute some importance to a certain category of the moderately sized particles (Sf_{10-20} lipoproteins) in the pathogenesis of atherosclerosis. They have moreover shown[5] that heparin is capable of transforming these particles into lipoproteins of smaller size, and they could reduce the degree of experimentally produced cholesterol atheromatosis in rabbits by injections of heparin.

In the course of investigations by Graham, Lyon, Gofman, Jones, Yankley, Simonton and White on the effect of heparin on lipoprotein metabolism,[5] Lyon and Yankley made the unexpected clinical observation that fifty-five of fifty-nine patients with moderate or severe angina pectoris stated that they felt pronounced improvement following injection of heparin, and that their use of nitroglycerin decreased considerably soon after treatment with heparin injections had been instituted. Forty-five of these patients (76 per cent) had previously had acute myocardial infarctions. They were treated for periods varying from one to eight months with one or two injections of from 50 to 100 mg. of heparin weekly, administered intravenously or intramuscularly. The alleviating effect on angina pectoris was usually observed after the first few injections. The authors were unable to offer any explanation for the possible relationship between the heparin effect on the lipoproteins of the blood and the alleviation of angina pectoris. The latter effect at any rate was not believed to be due to antithrombotic activity or vasodilatory action on the heart.

The object of the present work was to test the efficacy of the heparin treatment of angina pectoris.

MATERIAL AND METHODS

The patients treated were suffering from typical angina pectoris, provoked by the known factors and alleviated by nitroglycerin; none of the patients had congestive heart failure or valvular heart disease. Patients with syphilitic or rheumatic heart disease were excluded from the series. Twenty-seven patients in all were treated; three died in the course of treatment; these cases will be mentioned later. This leaves twenty-four patients who completed the treatment. The twenty-seven patients comprise twenty-one males and six females. The age varied from thirty-eight to sixty-nine years, averaging fifty-seven years. With regard to the duration of the disease, five had been ill for one year or less, eleven for two to three years and eleven for four years or more. Six of the patients (22 per cent) previously had had acute myocardial infarction.

The patients were treated as outpatients and were given two intravenous injections weekly. The patients were supplied with a card which they always carried with them to record daily the number and severity of attacks and the amount of nitroglycerin used. In order to form an estimate of the patients' ability to cooperate and the frequency of the attacks (in addition to what could be gathered from the case history at the first consultation), and also to determine

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whether the institution of treatment exerted any psychologic influence, they were given injections of a placebo (a pale, brownish sugar solution of the same appearance as heparin) during the first two to four weeks. Following this period 100 mg. of heparin* was given in each injection for a period varying from seven to eleven weeks; thus we used the same dosage as Graham et al.[5] The treatment was concluded by injections of the placebo for three weeks in order to determine whether the possible results of the treatment might be changed again.

Before treatment was instituted an x-ray was taken of the heart and lungs. An electrocardiogram and ophthalmoscopic examination were obtained immediately before and at the end of the intervening period during which heparin was administered. The patient's blood pressure was measured at each visit. The hemoglobin percentage and the weight were controlled in order to exclude any effects of anemia and fluctuations of the weight. Finally, we safeguarded against changes in the patients' daily routine, work, diet and consumption of medicine (in addition to nitroglycerin) which might give rise to erroneous estimates of the efficacy of the treatment.

In addition to angina pectoris five patients complained of intermittent claudication. This symptom, too, was closely followed during the heparin treatment, and oscillometry was performed before and toward the end of the heparin period.

Few side effects of the heparin treatment were observed. In one case there was troublesome bleeding from the incision of the ear after hemoglobin determination; hemorrhages from the site of the injection were observed in a few cases. One woman, aged fifty-four, had slight vaginal bleeding for twelve hours following each heparin injection.

RESULTS OF TREATMENT

The results of treatment were estimated first on the basis of the *frequency of the attacks* as recorded on the cards which the patients themselves filled in. A few of the patients were somewhat uncertain in recording their attacks, either because they were of the nature of attacks of dyspnea or oppression, or because they had only incipient attacks of angina pectoris which they were able to check in time. The following analysis of results applies to the twenty-four patients who completed the treatment; the three patients who died will be mentioned separately.

During the first few weeks when injections of the placebo were given a marked fall in the frequency of attacks was at once observed in most cases, in comparison with the frequency gathered from the case history; we did not attribute any great importance to this, however, as we were under the impression that the patients' statements about the frequency of attacks before treatment was instituted were of doubtful validity. With regard to the frequency of attacks during the entire period of treatment, the frequency decreased in nine patients, remained unchanged in twelve and increased in three.

As to the *severity of the attacks*, as indicated on the patients' cards, for the entire period of treatment, this decreased in twelve patients, remained unchanged in eleven and increased in one patient. Most of the changes in frequency and severity of attacks were very slight.

An analysis of the *subjective general impression of the patients* showed that fourteen patients considered that they had improved, ten that their condition remained unchanged. None of the patients thought that the condition had been aggravated.

Considering, finally, the *time in the course of treatment when improvement occurred*, eight of the fourteen patients who stated that they felt subjective improvement already felt improved during the first period of placebo injections, whereas only six stated that they felt better during the period when heparin was administered. This disclosure is of great importance in estimating the efficacy of heparin. It should be noted, moreover, that all fourteen patients except one who felt better during treatment stated that the improved condition remained unchanged during the last period when they were given injections of the placebo again.

Two of the three patients who died and who had been treated with heparin for periods from five to ten weeks had reported that their condition remained unchanged during treatment while the third had been feeling better during the first period of placebo injections.

Electrocardiograms recorded before treatment was instituted showed that fifteen patients had normal and nine had pathologic electrocardio-

* The heparin preparation used was kindly placed at our disposal by the A/S NOVO Terapeutisk Laboratorium, Copenhagen.

grams. By comparing the first with another recorded at the end of the period when heparin injections were given, the following changes were observed: Two of the fifteen essentially normal electrocardiograms showed improvement, eleven remained unchanged, and two showed worsening; one of the nine pathologic electrocardiograms showed improvement, six remained unchanged and two showed worsening. All the changes stated appeared in the T waves; there were no changes in the S-T segments or the QRS complexes. The only pathologic electrocardiogram which became normal in the course of the heparin treatment was that of a patient who had had an acute myocardial infarction two months before treatment was instituted. Thus no material change in the electrocardiograms could be demonstrated in the course of heparin treatment.

One of the authors who is an ophthalmologist (H. V.) examined the retinae of the patients (with complete mydriasis) on two occasions, without knowledge of the patients' age, blood pressure, stage of treatment or possibly complicating diabetes mellitus. On the second occasion his notes from the first examination were not available to him.

Vascular changes were observed in all twenty-four patients. In fourteen they were slight (eight of these patients had a normal blood pressure, six had hypertension); in ten patients the vascular changes were moderate (one of these had a normal blood pressure, nine had hypertension). Two patients had diabetes mellitus with characteristic diabetic retinopathy.

At the second examination of the eyegrounds the following changes were observed: two patients had improved, in seventeen the condition remained unchanged and in five there was worsening. All the changes stated were slight; in one patient, however, thrombosis occurred in a branch of one of the retinal vessels in the course of the heparin treatment. Thus changes in the ophthalmoscopical findings have not been demonstrated in the course of heparin treatment.

As already mentioned, the blood pressure was measured at each visit during the entire period of treatment. Nine of the twenty-four patients had a normal blood pressure before the heparin treatment and no changes occurred in the course of the treatment. Fifteen patients were hypertensive (the criterion was a systolic blood pressure of over 150 mm. Hg and a diastolic blood pressure of over 90 mm. Hg; it was required that both criteria be fulfilled). The blood pressure remained unchanged in twelve patients, two had a somewhat lower and one a slightly higher blood pressure during heparin treatment.

Summarizing, it can thus be said that only six of twenty-four patients stated that they felt improved during treatment with heparin and that no typical objective changes were found in the electrocardiogram, blood pressure or on examination of the eyegrounds which might be considered indicative of a beneficial effect of heparin.

Complication with Acute Myocardial Infarction and Death. As already mentioned, three of the patients died in the course of heparin treatment. The first was a man, aged fifty-six, who had stated that he felt doubtful improvement during the first period when the placebo was administered; he was then treated with heparin for three weeks. Four days after the last heparin injection he died in the hospital. The clinical diagnosis was acute myocardial infarction; unfortunately, autopsy was prohibited.

Another patient was a man, aged sixty-one, who stated that he felt distinct improvement during the first period of placebo injections; he was then given heparin injections for two weeks. Twenty-four hours after the last heparin injection he suddenly died in bed—presumably of acute myocardial infarction. The third patient, a man aged thirty-eight with xanthomatosis (Müller's syndrome), had been treated with heparin for ten weeks without any improvement. He died suddenly in bed three days after the last heparin injection. One patient was admitted to our department with acute myocardial infarction two weeks after the last period when placebo injections were administered.

Intermittent Claudication. As already mentioned, five patients complained of intermittent claudication; two of these patients stated that they felt improvement, one during the first period of placebo injections, the other not until heparin was administered. Oscillometric examination of these five patients—including the two who felt improved—showed no changes for the better when compared with the examinations before and at the end of the period of heparin injections.

COMMENTS

Of the twenty-seven patients who were treated fifteen thus stated that they felt subjective im-

provement. In nine of these cases, however, the improvement occurred at a time when the patients had only been given injections of the placebo. In these cases it is therefore reasonable to conclude that the psychologic effect of coming under new treatment with regular, careful control and questioning effected the improvement. We are inclined to believe that this was the case also in the six patients in whom the beneficial effect was said to have occurred only in the heparin period, and that it was quite accidental that these patients felt improvement only then. Possibly these few patients actually demonstrate a therapeutic effect of heparin. The fact that no aggravation was observed during the last period of placebo injections in five of these six patients is rather indicative that the effect was suggestive.

It may be mentioned that our examinations took place during the first half of the year, therefore, it is possible that some of the improvements recorded have been simply a consequence of the change in weather.

Heparin treatment might exert a beneficial effect without simultaneously demonstrable changes in the electrocardiogram, blood pressure or eyegrounds but the fact remains that it has not been possible by means of these objective methods to demonstrate favorable organic changes during the period of treatment.

Our results are at variance with those reported by Graham et al.;[5] they state that they have usually observed a dramatic decrease in the frequency of the attacks. It may be mentioned that we, too, observed a marked fall in the frequency of attacks when the frequency as estimated from the case histories as given by the patients was compared with the one recorded during the first period of placebo injections; but only in a small number of cases was a marked decrease in the frequency of attacks observed when we changed to heparin injections. In seven of fifty-nine patients who had at first been treated with heparin with good effect, Graham et al. changed to injections of a placebo; they state that the attacks then increased in frequency again. We consider that it is doubtful whether injections of a placebo in only seven of fifty-nine patients can afford sufficient information about the role which psychic factors may play in the course of treatment of a disease like angina pectoris, which is so susceptible to psychic influence.

It must also be considered whether the American series of cases and ours are comparable; they differ somewhat from each other, partly because the great majority of the American cases had had acute myocardial infarction before the treatment, partly because most of the American patients were younger (from forty to sixty years) than ours; in our series twelve patients were less than sixty years of age; only five of these stated that they felt subjective improvement, and this occurred in only one case during the heparin period.

SUMMARY

The object of this study was to examine the allegedly beneficial effect of heparin in the treatment of angina pectoris.

Twenty-seven patients with the anginal syndrome were treated ambulantly with intravenous heparin injections twice weekly. During the first two to four weeks placebo injections were given; this was followed by 100 mg. of heparin twice weekly for periods from seven to eleven weeks; finally, placebo injections were again given for three weeks.

Fifteen of twenty-seven patients stated that they improved during the period of treatment; nine of these improved during the first period of placebo injections whereas only six reported improvement during treatment with heparin.

We could not demonstrate typical objective changes in the electrocardiogram, blood pressure or ophthalmoscopic findings which might suggest a beneficial effect of heparin.

Three patients died of acute myocardial infarction during the treatment with heparin. One patient developed myocardial infarction two weeks after the end of the last placebo period.

Five patients suffered from intermittent claudication. Only one of these improved during treatment with heparin; no improvement could be demonstrated in the oscillometric indices.

We consider it improbable that treatment of angina pectoris with heparin in the recommended doses is of beneficial effect.

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Effect of Heparin in Effort Angina*

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RELIEF of angina pectoris by heparin was first reported in 1951 by Graham and his co-workers.[1] This finding was incidental to an investigation of the effects of heparin on the concentration of the serum lipoproteins (S_f 12–20 and 20–100). Efficacy of heparin in effort angina has since been reported by Engelberg,[2] while, on the other hand, no significant benefits were found by Russek[3] or by Miller, Zinn and Griffith.[4]

The present study was undertaken first to evaluate heparin in effort angina by the double blindfold method and the daily report card system for collecting data,[5] and secondly, to determine at the same time the effect of a course of heparin on the concentration of serum lipoproteins of the S_f 12–20 and S_f 20–100 classes.

METHODS

Observations were made on a group of eighteen patients with sclerosis of the coronary arteries and angina of effort, selected from about sixty patients with such a diagnosis who were carried in the active case load of the Cardiac Clinic. The selection was based on unequivocal evidence of coronary artery disease and on a history of chest pain produced by effort (usually walking) and relieved promptly by rest or nitroglycerin. Patients were excluded from the study because of variability or temporary remission of effort angina, cerebral arteriosclerosis or the inconvenience of coming to the clinic two or three times a week.

Sixteen patients were men; two were women. The ages ranged from forty-seven to seventy-nine years, with an average of 63.9 years. The duration of effort angina ranged from nine months to seventeen years, with an average of six years. Ten (55 per cent) of the patients were known to have had a previous myocardial infarction. No patient had had an acute myocardial infarct within six months prior to the start of the investigation. Three patients had hypertension; the levels were 160/100, 170/100 and 150/100 mm. Hg, respectively. Not one of the patients was obese. The average weight was 140 pounds, with a range of 120 to 165 pounds. No patient had a history of any hemorrhagic episode.

During the control period each patient had the following baseline evaluation: resting 12-lead electrocardiogram, resting ballistocardiogram,‡ fluoroscopy or x-ray of the heart and lungs, retinal examination, determination of the serum cholesterol, serum lipoproteins of the S_f 12–20 and S_f 20–100 classes,§ blood sedimentation rate, complete blood count, urinalysis and heparin clotting time. An abnormal electrocardiogram was present in fourteen patients (77 per cent) and an abnormal ballistocardiogram in fifteen patients (83 per cent). No patient had both a normal ballistocardiogram and a normal electrocardiogram.

‡ Ballistocardiograms (taken with the Glennite instrument of the John Peck Laboratories, New York, N. Y.) were recorded simultaneously with lead I of the electrocardiogram on a two-channel direct-writer electrocardiograph (made by the Sanborn Co., Cambridge, Mass.).

§ These determinations were made by the Belmont Laboratories, Belmont, Calif. The blood samples were drawn several hours after lunch (with no restrictions as to diet), and the tests were carried out within forty-eight hours.

* From the Department of Pharmacology, Cornell University Medical College, and the Cardiovascular Research Unit, Beth Israel Hospital, New York, N. Y. This investigation was supported (in part) by research grants from the National Heart Institute of the National Institutes of Health, Public Health Service, the Loyal League Philanthropies, New York, N. Y., and the Upjohn Company, Kalamazoo, Mich.

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The patients were observed for approximately two months prior to heparin administration, that is, for a long enough period to record the baseline of chest pain. During this period the extent of the somatic component of cardiac pain[6–11] was evaluated and an attempt was made to eliminate trigger areas in the chest muscles which might serve as additional sources of chest pain. When such trigger areas were found (sixteen patients), ethyl chloride spray was applied to the chest twice weekly by a special technic.[12,13] In some instances procaine infiltration of these trigger areas was carried out.[7,14] This type of local block therapy was continued until trigger areas disappeared or until it was apparent that maximum benefits had been achieved.

To secure two parallel series the eighteen patients were paired as closely as possible with respect to sex, age, duration of effort angina and history of myocardial infarction. One woman was allotted to each group. The average age for the two groups was 63.6 and 64.3 years, the average duration of effort angina was 6.4 and 5.7 years, and the incidence of previous myocardial infarction was 66.7 and 44.4 per cent, respectively. The basis for pairing is shown in Table 1; the levels of serum lipoproteins varied too widely to permit matching on this basis. To randomize the series one of each pair was allotted by chance to one of the two groups; one group received heparin and the other a placebo. Fortuitously one of the three hypertensive patients was in the heparin group and the other two were in the placebo group.

To eliminate the factor of unconscious bias the double blindfold method was employed throughout. This meant that the study was conducted by a team, and that not merely the patients but also the physicians who questioned and examined them, injected the solutions and later assessed the data were unaware of the nature of the coded solution given to any particular patient.

TABLE 1

CLINICAL DATA ON PAIRED PATIENTS WITH EFFORT ANGINA AND ARTERIOSCLEROTIC HEART DISEASE*

Heparin Group									Placebo Group							
Patient			Duration of Angina (yr.)	Old Myocardial Infarct	Resting		Lipoproteins Initial Level		Patient			Duration of Angina (yr.)	Old Myocardial Infarct	Resting		Lipoproteins Initial Level	
No.	Age (yr.)	Sex			ECG†	BCG	S_f 12–20 (mg. %)	S_f 20–100 (mg. %)	No.	Age (yr.)	Sex			ECG	BCG	S_f 12–20 (mg. %)	S_f 20–100 (mg. %)
1	47	M	1	no	N.	Abn.	18	65	10	52	M	1	no	Abn.	N.	34	114
2	61	M	¾	yes	Abn.	N.	22	46	11	66	M	1	no	N.	Abn.	30	96
3	58	M	12	yes	Abn.	Abn.	18	57	12	53	M	9	yes	Abn.	Abn.	43	89
4	79	M	11	yes	Abn.	Abn.	11	12	13	76	M	4	no	Abn.	Abn.	44	116
5	67	M	3	yes	Abn.	Abn.	20	113	14	75	M	3	yes	Abn.	Abn.	18	40
6	59	M	17	yes	Abn.	Abn.	106	247	15	59	M	17	yes	Abn.	Abn.	30	79
7	59	F	4	no	N.	Abn.	40	69	16	52	F	6	yes	Abn.	Abn.	102	273
8	74	M	2	no	Abn.	Abn.	32	33	17	76	M	8	no	Abn.	Abn.	73	135
9	68	M	7	yes	Abn.	N.	18	95	18	70	M	2	no	N.	Abn.	16	48

* Based on the criteria of the New York Heart Association[15]
† N. = normal; Abn. = abnormal

Two materials* were compared in this study: sodium heparin, which was injected intravenously twice weekly in doses of 100 mg. (1 cc.) and 1 cc. of a placebo solution similarly administered. The placebo solution matched the heparin solution in color and viscosity. Heparin and placebo were given *concurrently* to the matched groups, the heparin for an average of 9.4 weeks (8 to 11 weeks) and the placebo for an average of 8.3 weeks (6 to 10 weeks).

The average number of doses of heparin per patient was eighteen (fifteen to twenty) and the average number of doses of the placebo was sixteen (ten to twenty). No patient missed more than one or two doses except Case 15 in the

* The heparin and matching placebo solutions were supplied by the Upjohn Company, Kalamazoo, Mich. The placebo solution contained approximately 4.5 per cent gelatin and 2.0 per cent dextrose anhydrous in water, preserved with 0.4 per cent chlorobutanol; the slightly brownish color resulted from autoclaving the dextrose.

placebo group: this patient missed seven injections but came to the clinic at least once a week. This concurrent method of administering the test drug and the placebo was chosen because environmental and seasonal factors are controlled in this way.

whether he had some heart pain (an average good day), a great deal of heart pain (a bad day) or a day with no heart pain at all. He also indicated on the card the number of nitroglycerin tablets taken each day and each night.

Heparin clotting times[16,17] were determined

TABLE II

CONCENTRATION OF SERUM LIPOPROTEINS FOR HEPARIN AND PLACEBO GROUPS

Case No.	Before Injections		3 Weeks after Start of Injections		6 Weeks after Start of Injections	
	S_f 12–20 (mg. %)	S_f 20–100 (mg. %)	S_f 12–20 (mg. %)	S_f 20–100 (mg. %)	S_f 12–20 (mg. %)	S_f 20–100 (mg. %)
Heparin Group						
1	18, 18 * 18	61, 68 * 65	23	60	14	46
2	22	46	..	...	23	43
3	18	57	26	66	13	48
4	8, 14 † 11	5, 18 † 12	..	...	8	9
5	20	113	..	...	14	74
6	93, 118 † 106	292, 202 † 247	96	182	98	300+
7	40	69	..	...	27	21
8	32	33	..	...	23	33
9	18	95	34	150	33	203
Averages	31.7	81.9	..	...	28.1	86.3
				Net Change	−11.4%	+5.4%
Placebo Group						
10	34	114	..	...	20	63
11	30	96	..	...	24	18
12	43	89	44	83	46	58
13	44	116	..	...	...	...
14	18	40	17	36	19	32
15	30	79	36	63	28	36
16	98, 106 † 102	306, 240 † 273	97	226	84	229
17	73	135	..	...	41	79
18	16	48	..	...	12	40
Averages	43.3	110.0	..	...	34.3	69.4
				Net Change‡	−20.8%	−36.1%

* Duplicate determinations on same sample of blood, submitted under different names

† Determinations made on 2 samples of blood drawn one week apart

‡ Excluding Case 13

The effect of these agents on cardiac pain was evaluated from data obtained from the daily report card.[5] In essence the method was as follows: the patient was given a card upon which he recorded at the end of each day, by marking an X in the appropriate column,

prior to the administration of heparin or placebo and at intervals in order to study individual susceptibility to the anticoagulant.*

* This part of the study was directed by Dr. Robert L. Rosenthal and the results will form the subject of another report.

Three weeks after starting the injections of heparin and placebo, determinations of the serum lipoproteins were repeated on eight patients who showed at that time a change in the status of cardiac pain (either better or worse). Four were in the heparin and four in the placebo group. Six weeks after the administration of these agents was begun this test was repeated on the entire series, except for one patient who received the placebo (Table II, Case 13).

Electrocardiograms and ballistocardiograms were repeated on all patients at the end of the study.

TABLE III

EFFECT OF HEPARIN AND PLACEBO ON EFFORT ANGINA BASED ON ANALYSIS OF 1,883 REPORT CARD DAYS

	Heparin Group				Placebo Group			
	Number of Report Card Days				Number of Report Card Days			
	Total	Good	Bad	Pain-free	Total	Good	Bad	Pain-free
Control period	497	280 (56%)	111 (22%)	106 (22%)	375	294 (78%)	40 (11%)	41 (11%)
Injection period	533	355 (67%)	97 (18%)	81 (15%)	478	369 (77%)	78 (16%)	31 (7%)

RESULTS

Cardiac Pain. The effects of heparin and placebo on cardiac pain are summarized in Table III. During the control period the patients receiving heparin reported on 497 days, 56 per cent of which were described as good, 22 per cent as bad and 22 per cent as entirely free from heart pain. During heparin administration the same group reported on 533 days, 67 per cent of which were good, 18 per cent were bad and 15 per cent were pain-free. In comparing these figures for control and treatment periods it is evident that after heparin the incidence of bad days was essentially unchanged, while the good days increased but at the expense of the pain-free days. This change is not statistically significant. The patients receiving the placebo reported on 375 days during the control period, 78 per cent of which were good, 11 per cent bad and 11 per cent pain-free. During the period of placebo administration the same patients reported on 478 days, 77 per cent of which were good, 16 per cent bad and 7 per cent pain-free. Thus during the administration of the placebo as compared with the control period the incidence of good days remained the same while the per cent of bad days increased slightly at the expense of the pain-free days. This difference likewise is not statistically significant.

It occurred to us that possibly there was a lag in the development of the beneficial effect of heparin which might be masked in the averages cited for the entire heparin period. An analysis was therefore made of the good, bad and pain-free days for the first four weeks (242 report card days) and last four weeks (248 report card days) of heparin administration. No significant difference was found. Thus the incidence of good days was 70 per cent for the first four weeks and 65 per cent for the last four weeks of heparin administration; the incidence of bad days was 18 per cent for the early period as compared with 20 per cent for the late period, and the incidence of pain-free days was similarly 12 per cent as compared with 15 per cent.

It may be seen from Table IV that the average number of nitroglycerin tablets used per week by the heparin group decreased slightly (from 14.6 tablets during the control period to 12.4 tablets during the injection period) and for the placebo group increased slightly (from 16.1 tablets during the control period to 20.3 tablets during the injection period). The changes in neither group are statistically significant ($p > 0.2$ and > 0.5, respectively).

Cardiograms. Electrocardiograms taken at the end of the series of injections revealed no

deviation from the initial graphs. The ballistocardiograms likewise remained the same except for one patient in the placebo group (Case 12) in whom an abnormal ballistocardiogram became normal (taken on three occasions).

TABLE IV
EFFECT OF HEPARIN AND PLACEBO ON USE OF NITROGLYCERIN TABLETS BASED ON ANALYSIS OF 1,883 REPORT CARD DAYS

Heparin Group			Placebo Group		
	Number of Tablets Used			Number of Tablets Used	
Case No.	Control Period (av./wk.)	Injection Period (av./wk.)	Case No.	Control Period (av./wk.)	Injection Period (av./wk.)
1	37	33	10	0.4	0.3
2	6	4	11	6	4
3	33	27	12	7	5
4	5	5	13	14	2
5	4	8	14	13	17
6	41	30	15	65	122
7	0	0.2	16	1	3
8	0	0	17	33	24
9	5	5	18	6	6
Averages	14.6*	12.4*	Averages	16.1†	20.3†

*$t = p > 0.2$
†$t = p > 0.5$

Serum Lipoproteins. Table II lists the values for serum lipoproteins determined during the course of the study. In the heparin group the average control level of the serum lipoproteins was 31.7 mg. per cent for the S_f 12–20, and 81.9 mg. per cent for the S_f 20–100 class, respectively. Similarly, in the placebo group the level was 43.3 mg. per cent for the S_f 12–20, and 110.0 mg. per cent for the S_f 20–100 class. Six weeks after heparin was begun the average value for the S_f 12–20 class had fallen to 28.1 mg. per cent (−11.4 per cent), and for the S_f 20–100 class had increased to 86.3 mg. per cent (+5.4 per cent). In comparison six weeks after starting the placebo injections the serum lipoproteins had diminished to 34.3 mg. per cent (−20.8 per cent) for the S_f 12–20, and to 69.4 mg. per cent (−36.1 per cent) for the S_f 20–100 class. The t test was applied and showed that the only statistically significant change in the averages was the 36.1 per cent reduction in the S_f 20–100 class in the placebo group ($p < 0.01$).

With respect to the direction of change at the end of the six-week period two patients in the heparin and two in the placebo group showed an increase in the level of serum lipoproteins for the S_f 12–20 class; for the S_f 20–100 class two patients in the heparin group and none in the placebo group showed an increase. The individual curves, together with the averages, are plotted in Figure 1.

Heparin Clotting Time. The control heparin clotting times[16,17] were normal in all but two patients. One of these (Case 2) had a slightly rapid clotting time and in the other (Case 4) it was prolonged. Both these patients received heparin subsequently.

Side Actions. No bleeding or thrombotic complication occurred in any patient during the course of the injections. One patient had an acute myocardial infarction one month after the last dose of heparin. It is interesting that this was the patient with the initially prolonged heparin clotting time and the lowest levels of the serum lipoproteins (S_f 12–20: 8, 14 and 8 mg. per cent; S_f 20–100: 5, 18 and 9 mg. per cent—Table II, Case 4).

Three patients complained of dizziness at once or a few hours after an injection; one received heparin and the other two the placebo. Another patient complained of postinjection headache which appeared for a few hours after each dose during the first two weeks of the injection period; this patient received the placebo.

COMMENTS

The steps by which heparin came to be used in the treatment of effort angina were as follows: It was first demonstrated that heparin abolishes alimentary lipemia.[18–23] Secondly, while investigating the relationship between atherosclerosis and serum lipoproteins of the S_f 10–100 class in rabbits, the California group[1] showed that the daily injection of heparin for three to eight weeks prevented atherosclerosis and suppressed the development of molecules of the S_f 10–50 class. Subsequently these findings were applied to man and it was observed[1] that the intravenous injection of a single dose of 100 mg. of sodium heparin in a patient with a myocardial infarction and a high level of serum lipoproteins of the S_f 10–20 and 20–100 classes caused a prompt shift of the lipoprotein molecules from the higher to the lower S_f classes. This was an acute effect which reverted to the initial pattern within twenty-four hours. Graham et al.[1] then administered heparin intravenously to twenty patients at intervals of two to fourteen days. These investigators noted that "a small proportion of the patients showed depres-

sion in S_f 10–20 levels which persisted for the full three to fourteen day intervals between intravenous injections of heparin, but in general the levels observed 3 to 14 days after injection showed no average trend toward reduction." They stated, on the other hand, that they had namely, the *averages* showed no significant lowering of the serum lipoproteins of the S_f 12–100 classes although some patients did show a final reduction in these molecules. In our series the percentage change from the initial levels to those found six weeks after starting heparin was

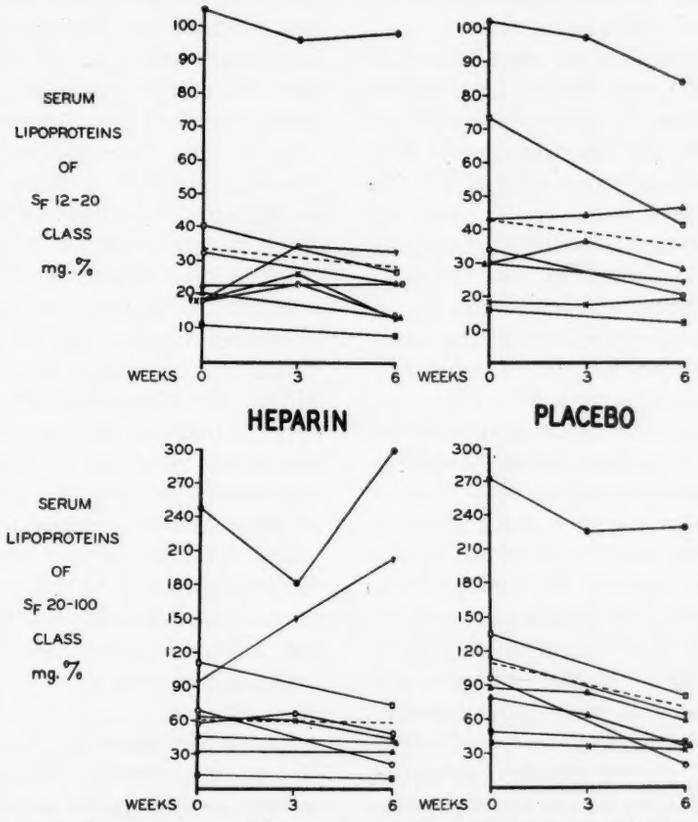

FIG. 1. Level of serum lipoproteins of the S_f 12–20 and S_f 20–100 classes during control period and at three and six weeks after start of injections (heparin or placebo). Solid lines show values for individual patients; broken lines indicate averages (omitting the three-week intermediate values).

"direct evidence that with a suitable heparin dosage schedule, chronic lowering of the serum S_f 10–20 levels can be obtained." To substantiate this one patient is described who for one month maintained an S_f 10–20 depression for the three-day intervals between heparin injections (100 mg. each) and on cessation of the heparin injections showed a slow, progressive rise over a one-month period to a level which approached the original S_f 10–20 concentration. A second patient is mentioned who received 100 mg. of heparin by vein daily for four weeks and showed a similar effect.

These observations[1] on the chronic effect of heparin given intermittently in doses of 100 mg. each are exactly in agreement with our findings, -11.4 per cent for the S_f 12–20 and $+5.4$ per cent for the S_f 20–100 class. (Table II.) Further analysis shows that six of the nine patients given heparin showed a reduction of 20 per cent or more for the S_f 12–20 class, and four patients showed a reduction of 20 per cent or more for the S_f 20–100 class.

The point of interest in our study is that the patients who received only placebo injections showed an even larger reduction in the values of the serum lipoproteins, namely, a change of -20.8 per cent for the S_f 12–20, and -36.1 per cent for the S_f 20–100 class. So far as the individual cases are concerned a final lipoprotein value was obtained on eight of the nine patients given the placebo; in this group a reduction of

20 per cent or more for the S_f 12–20 class occurred in four of the patients and for the S_f 20–100 class, in six. This points up again the necessity for proper controls in such studies, for had our placebo and heparin groups been fortuitously reversed the striking change which occurred spontaneously in the lipoprotein levels would have been attributed to heparin.

We are at a loss to explain the significant fall in the lipoproteins of the S_f 20–100 class which was noted after six weeks on placebo injections. Since Gofman and Jones[24] reported a relationship of the lipoproteins, especially of the S_f 35–100 class, to obesity, we attempted to correlate this change in the lipoproteins with changes in the body weight of our patients. However, there was practically no change in weight either on the average or for the individual members of the heparin or placebo groups during the injection periods.

Another effect that has been attributed to heparin is the relief of angina pectoris. Graham and co-workers[1] indicated that fifty-five of fifty-nine patients with moderate or severe angina pectoris reported marked relief from this symptom with a drastic decrease in nitroglycerin requirement soon after starting heparin injections. These patients received one or two injections of 50 to 100 mg. of sodium heparin per week. The injections were given intravenously or intramuscularly for periods of one to eight months. Relief from angina usually was noted after the first few injections. All of seven patients whose severe angina had been relieved by heparin injections complained of return of anginal symptoms when saline placebos were substituted for heparin. Graham et al.[1] could not correlate this relief of pain with the effect of heparin on the serum lipoproteins. Engelberg[2] treated twenty-nine patients with severe angina pectoris with 25 to 100 mg. of heparin given intravenously twice a week. Heparin was given for six to twelve months with control periods of saline injections. The clinical response was evaluated on the basis of their weekly nitroglycerin intake. Heparin reduced effort pain in 55 per cent of the patients. The relief of pain was accompanied in some cases by improvement in the exercise electrocardiograms and in the ballistocardiograms.

Negative results, however, have been reported by other investigators. Russek and co-workers[3] found in fourteen patients with coronary insufficiency, nine of whom had classic effort angina, that the administration of heparin over relatively short periods was without significant effect on the electrocardiographic response to standard exercise as measured twenty-four hours after the initial dose of heparin and daily thereafter so long as heparin was given. The average number of injections of the drug was 3.3 (range 1 to 7), the route was intravenous, and the dose 100 mg. except in two patients who received doses of 50 mg. Their observations are of interest because in their control studies all of the patients were shown to be capable of registering electrocardiographically a coronary dilator response to nitroglycerin; that is, a test dose of nitroglycerin prevented the S-T segment or T-wave changes induced by the exercise. In two patients it was found further that heparin had no nitroglycerin-like effect on the response to exercise either immediately or six or twelve hours later. Miller, Zinn and Griffith[4] injected 100 mg. of heparin intramuscularly three times a week for six weeks, and then 2 cc. of normal saline solution three times a week for six weeks, in a group of patients with angina pectoris. In a second group the order of the injections was reversed. All patients were started on therapy at the same time. Under double blindfold methods of study the placebo proved at least as effective as heparin, and possibly more effective, in relieving effort angina.

Our study takes its place in the latter series of negative reports. The question arises again in the case of heparin as to how such contradictory conclusions regarding the therapeutic value of a drug can occur. We believe that the answer lies in the kinds of safeguards which have been applied to control all possible sources of error. The use of such safeguards distinguishes the valid investigation in clinical pharmacology from the mere clinical trial of a drug.[25,26] These safeguards include the use of a matching placebo and a double blindfold technic; the choice of a suitable indicator of clinical effect; the selection of case material to include only patients appropriate to the problem under study; either the setting up of comparable groups for placebo and test drug, or a plan of rotation of placebo and test drug in each patient if carry-over effects are not suspected; and, finally, the application of statistical checks to the data.

Our study differs from the above positive reports[1,2] first in that we used a double blindfold method. The investigations which reported favorable results with heparin in effort

angina made no mention of the double blindfold method of study, even though a placebo was used. In the negative reports only that of Miller, Zinn and Griffith[4] utilized the double blindfold principle.

In the second place the indicator of effect which we employed in evaluating heparin in angina pectoris was the patient's daily statement concerning his cardiac pain.[5] In this daily report card system the patient notes at the end of each day whether he has had as much heart pain as usual, more than usual or less than usual (or none at all).

An indicator of effect commonly utilized in studies on effort angina is the daily intake of nitroglycerin tablets.[2,4] Although we observed no significant change in the average number of such tablets taken during either heparin or placebo administration (Table IV), we consider that in our series of patients the number of nitroglycerin tablets taken is a less reliable index of therapeutic effect than is the daily reporting of pain because our subjects were not especially selected on the basis of their response to nitroglycerin. Our data suggest that too many variables other than pain determined the frequency with which these patients used nitroglycerin. For example some patients (Cases 7, 8 and 10) had effort angina but practically never took nitroglycerin; conversely, one patient (Case 15) used nitroglycerin freely although his attacks were apparently no more severe than theirs. Furthermore the best response to therapy in terms of nitroglycerin occurred in the patient (Case 13) who had a seven-fold reduction in the number of tablets used while receiving placebo injections. If the response to nitroglycerin is to be used as an index of the effect of therapy in angina pectoris, care should be exercised to insure that all subjects in the study habitually use nitroglycerin whenever they have pain and habitually experience prompt relief.

Changes in the electrocardiogram affecting the S-T segments and the T-waves after exercise[3] or after breathing low concentrations of oxygen have been used as indicators of hypoxia of the myocardium. We did not employ such tests in this investigation for a number of reasons. When a drug prevents the hypoxic electrocardiographic changes in a patient with effort angina, the conclusion is often drawn that this drug must also be effective in preventing the effort pain which the patient experiences.[27,28] That this inference does not necessarily follow has been shown by the failure of such drugs as cytochrome C[29] and khellin[5,30] to relieve effort angina clinically, even though they may prevent the electrocardiographic changes usually induced by the aforementioned stress tests.

Exercise tests with pain as the end point[31,32] have also been used to evaluate the efficacy of drugs in angina pectoris. Greiner and coworkers[5] have pointed out that values obtained in this way may not apply to the effort angina of patients when they function in their habitual manner. They state, "There seems to be no ready escape from dependence on the modality of pain in its natural habitat in exploring drugs for the control of pain of angina of effort." Beecher[26] more recently has reviewed the inherent differences between experimental and pathologic pain.

The diagnosis of angina pectoris depends on the history of chest pain on effort and not on any laboratory test now available. In the selection of patients, therefore, we relied mainly on such a history. In order to insure the validity of the history the patients were observed during a control period of several weeks and were repeatedly interrogated with regard to the detailed characteristics of their pain. Corroboration of the cardiac etiology of effort pain was afforded by the fact that every patient had either evidence of coronary artery disease in the resting electrocardiogram or an abnormal ballistocardiogram.

In addition, because of the resemblance of some pain syndromes of the chest muscles to effort angina,[8] we made an evaluation of somatic sources of chest pain. By this we refer not only to the musculoskeletal pain which results from such environmental and mechanical stresses as sudden trauma, bad posture and chronic overuse of the muscles, but also to the somatic component of cardiac pain,[7] namely, the development of trigger areas in the chest muscles as the result of visceromotor reflexes from the ischemic heart muscle. It is important to recognize that once it is initiated this secondary pain syndrome based on spasm of the somatic musculature may persist independently and may either mimic or summate with true cardiac pain.[7,8,33] After evaluating its extent we attempted to reduce or eliminate the somatic component so that any effect of heparin on the pain due to coronary insufficiency would not be masked by the dominance of somatic chest pain.

For example one patient (Case 1) averaged forty-nine nitroglycerin tablets per week during the first five weeks of the control period. During this time the chest was sprayed with ethyl chloride and the trigger areas in the chest muscles were infiltrated with procaine biweekly. Coincident with the elimination of the somatic trigger areas his consumption of nitroglycerin decreased and during the ensuing four weeks of the control period averaged only twenty-three tablets per week. Heparin was then given during the following eight weeks. The average for the first seven weeks on heparin injections was twenty-five tablets per week. Such a control in the preparation of the patient is, we believe, unique in the study of the effects of drugs in effort angina.

SUMMARY AND CONCLUSIONS

The effect of heparin on effort angina of patients with arteriosclerotic heart disease was compared with that of a matching placebo by means of the double blindfold method. The eighteen patients selected for the study were paired with respect to age, sex, duration of effort angina and incidence of myocardial infarction, and were then divided at random into two parallel series. During the control period any possible masking of a change in effort angina by the somatic component of cardiac pain was minimized by local treatment of trigger areas in the chest muscles. Heparin was then administered to one group of nine patients while the placebo was given concurrently to the other group of nine. These agents were injected intravenously twice weekly over a period of eight to nine weeks. Each dose of heparin was 100 mg.

The effect of the injections on effort angina was judged by the daily report card system (the patient's day-to-day evaluation of cardiac pain) and by the average number of nitroglycerin tablets used per week. Resting electrocardiograms and ballistocardiograms were taken before and after the course of injections.

The results, based on the analysis of 1,883 report card days recorded by eighteen patients, show that heparin has no greater effect than a placebo in the control of effort angina.

A comparison of the levels of serum lipoproteins of the S_f 12–20 and S_f 20–100 classes showed no significant change in concentration after six weeks of heparin or placebo administration, except for the S_f 20–100 class in the placebo group which showed a significant fall (−36.1 per cent). This fall could not be attributed to variations in the weights of the patients while on placebo injections.

Side actions consisted of dizziness and headache; their incidence was slightly higher in the placebo than in the heparin group. These side actions did not necessitate stopping the medication.

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Review

Edema of Acute Nephritis*

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THE frequency and importance of heart failure as a feature of acute glomerulonephritis has been repeatedly emphasized.[1–12]† In general these reports confirm the opinion of Volhard:[1] "The clinical picture of acute diffuse glomerulonephritis, therefore, may present itself in the form of an acute and most severe insufficiency of the heart with dyspnea of the highest degree, increase of the venous pressure and swelling of the liver. Almost every case that dies in the acute stage of the disease dies of cardiac insufficiency through overdilatation." The role of heart failure in the production of the functional disturbances that characterize the disease, especially edema, have, however, received less attention. A consistent correlation with edema is evident in several of the reports[6,8–11,13] but has usually provoked no especial remarks or been regarded as adventitious. Levy[13] and Bradley[12] admit that when heart failure occurs it may play a contributory role in the production of edema. La Due,[8] from a direct investigation of the cardiac status in relation to edema in twelve patients with acute glomerulonephritis, concluded that heart failure offered the best explanation for the edema that attended the condition. The series was small but intensively studied and well controlled. The evidence for the association of edema with heart failure in these cases was convincing. An attempt has been made in a larger and more varied series of cases to evaluate the role of heart failure in the production of edema in acute glomerulonephritis and to weigh it against other features of the disease to which responsibility for the edema has been attributed.

MATERIAL

The material consists altogether of 291 patients with acute nephritis who have been seen in the New Haven Hospital in the course of the last thirty years and studied to varying degrees. The analysis is chiefly statistical and confined to the condition of the patients upon admission to the hospital (or at the onset of the disease, if this arose in the hospital) and the immediately subsequent period. Patients in whom there was convincing evidence of chronic disease were excluded, with exceptions which will be mentioned; but in case of doubt, patients were included in order to avoid, so far as possible, any chance of prejudice. In addition, with the exceptions to be mentioned, no patients who had had the disease more than six months were included. The great majority were in the first few days of the disease; according to their histories all were in their first attacks.

The exceptions referred to were forty-two patients in a condition which will be termed for convenience the nephrotic syndrome. Actually the term "hypoalbuminemic" might be more appropriate since the criteria which, for these purposes, distinguish them are that serum albumin was 2.1 per cent or less, or when proteins were not fractionated, total protein was less than 4.5 per cent. These may seem arbitrary figures and somewhat high by present standards. The serum proteins of the earlier patients in the series were fractionated by Howe's[14] method. It is now recognized that this method yields too high values for serum albumin. General experience had led to the conclusion that without rigorous treatment, edema of nephritis could not be prevented if serum albumin measured by this method was 2.0 per cent or less. Since 1947 Milne's[15] modification of Majoor's[16] method has been employed. This yields lower and more precise values for albumin; hence the "critical" concentration of albumin for the occurrence of edema appears to be lower. This has been taken into consideration. In cases in which the Milne method has been employed serum albumin far lower than 2.0 per cent has been used as a criterion for the diagnosis of the nephrotic syndrome.

† References to the subject are so numerous that only a few from the recent literature are cited. These cover the major points and will enable the reader to find other significant reports.

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All but one of these patients had edema at the time of observation. They were included in the series for several reasons. The history of many extended only a few days before admission, although it was obvious from their clinical condition that the disease was of much longer duration. These could not properly be excluded; but it was equally improper to include them while excluding cases that were clinically comparable but had more reliable histories. In addition all of these patients exhibited a condition in which "renal" edema had a clearly demonstrable cause, for comparison with "renal" edema without hypoalbuminemia, the cause of which was obscure.

The total series was composed of 194 men and ninety-seven women, reflecting the well known discrepancy in the sex incidence of the disease. The age of the patients ranged from one to seventy years. Patients were included irrespective of the presence or absence of edema, in order that the features that distinguished the two groups could be analyzed. Of the 194 men, 109 (56 per cent) had edema; of the ninety-seven women, fifty-eight (60 per cent) were edematous. In the edematous category are placed not only patients with obvious pitting of dependent regions of the body but also those who had recognized puffiness confined to the eyes and face and those who, without subjective or objective evidence of edema, lost an otherwise unaccountable amount of weight.

METHODS

The observations on which this evaluation is based are quite diverse; the patients were not all subjected to uniform types of examination or treatment. For the great majority only the usual clinical examinations are available. In a considerable number many special investigations were made. Some of these have no direct bearing on the present questions or were not done at precisely the time of the cardiac evaluation. Recently, because more interest in the subject has been aroused, patients have been studied in more detail. Nevertheless, since such studies can not be allowed to compromise the care of patients, complete assessment of cardiac function is often still impossible. The diagnosis of heart failure, however, even in the best clinics is in most cases made without special aids. The general procedure has been to check against the presence or absence of edema the various signs and symptoms that are significant in the diagnosis of heart failure. Only a fraction of the patients can be used for any single comparison but every patient about whom any relevant evidence was available has been included in the comparisons. No two of the tabulations contain exactly the same subjects.

The criteria of heart failure were: (1) dyspnea, orthopnea, basilar rales, pleural effusion, enlargement of the heart and enlargement of the liver found by physical examination; (2) enlargement of the heart, pulmonary congestion and pleural effusion found by x-ray; (3) significant changes in the electrocardiogram (electrocardiographic changes were given little weight because they can not be related directly to heart failure. They are, however, evidences of some cardiac disorder and therefore relevant to an evaluation of the cardiac status); (4) increased venous pressure or prolonged circulation time, or both; (5) diuresis after administration of digitalis. Certain other signs are not included in the analysis either because they would overload the article out of proportion to their importance or because they had not been recorded with sufficient frequency or care. Among signs of the latter category is the presence or absence of distention of the neck veins, which would offer a valuable comparison with venous pressure. Although it was undoubtedly frequently observed, it was seldom recorded. No single criterion was considered diagnostic of heart failure.

RESULTS

Non-protein Nitrogen of the Blood. So far as the severity of the disease, especially with respect to impairment of renal function, is concerned, there is no sharp distinction between edematous and non-edematous patients. This is clear from Figure 1 in which blood non-protein nitrogens of edematous and non-edematous patients are compared. There is no striking difference in the distribution of patients in the two categories. A similar lack of correlation could be shown if other indices of renal insufficiency were used, but non-protein nitrogen has been selected because it was measured in the largest proportion of patients.

Blood Pressure. In Figure 2 the presence and absence of edema are compared with systolic and diastolic blood pressure. The spread of blood pressure may be somewhat greater in the edematous group, in which the highest and the lowest figures are found for both systolic and diastolic pressures. The distribution of the edematous group also seems to be skewed to the left in com-

parison with the non-edematous. This latter feature can be ascribed partly to inclusion of the patients with the nephrotic syndrome. If these were omitted, the general distribution of the two groups would be more similar. Although the peaks of the edematous cases would still lie slightly to the right of the non-edematous peaks, the difference would not be striking. At best there is not sufficient correlation between hypertension and edema to vitiate comparisons of the two groups.

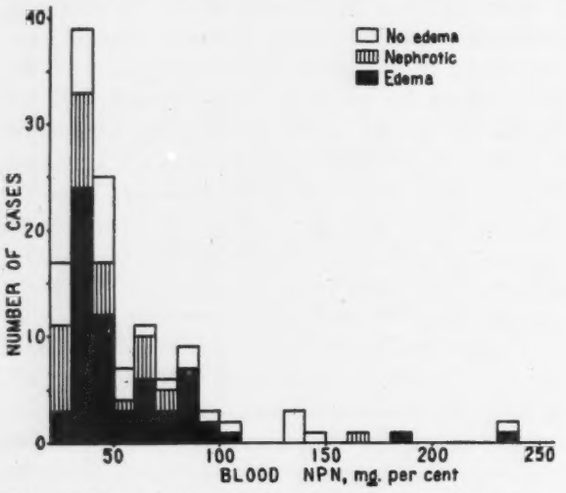

FIG. 1. The relation of blood non-protein nitrogen to edema. All nephrotic patients were edematous.

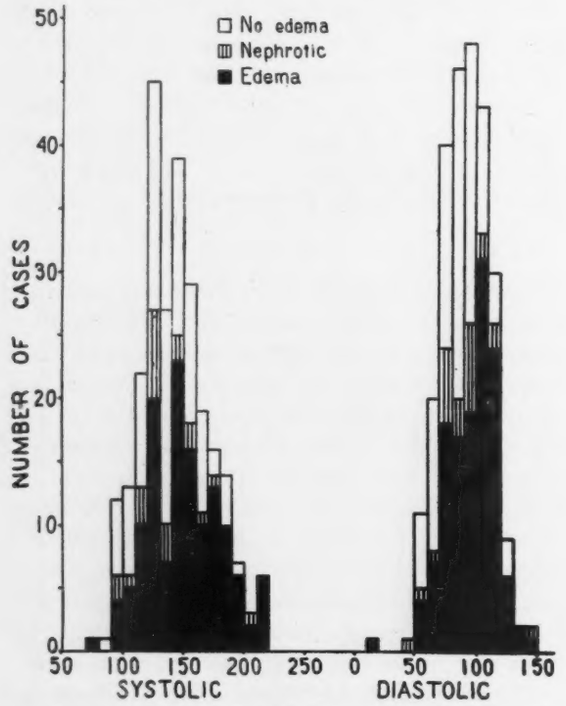

FIG. 2. The relation of blood pressure to edema. All nephrotic patients were edematous.

Serum Proteins. In Figure 3 edema is compared with the concentration of protein in the serum. Total protein has been used for this comparison rather than serum albumin because, as was stated earlier, in the course of this study the procedure for fractionation of protein was changed and the two methods give different values for albumin but identical values for total protein. Since disturbances of globulin were seldom important and usually not reciprocally related to those of albumin, total protein serves present purposes and permits the inclusion of a larger number of patients. It is evident from the figure that in the early or acute stages of the disease there is little correlation between serum protein and the incidence of edema; in this stage edema may occur while protein is quite normal. Serum albumin is seldom low enough to become an important element in the production of edema until nephritis has persisted for three

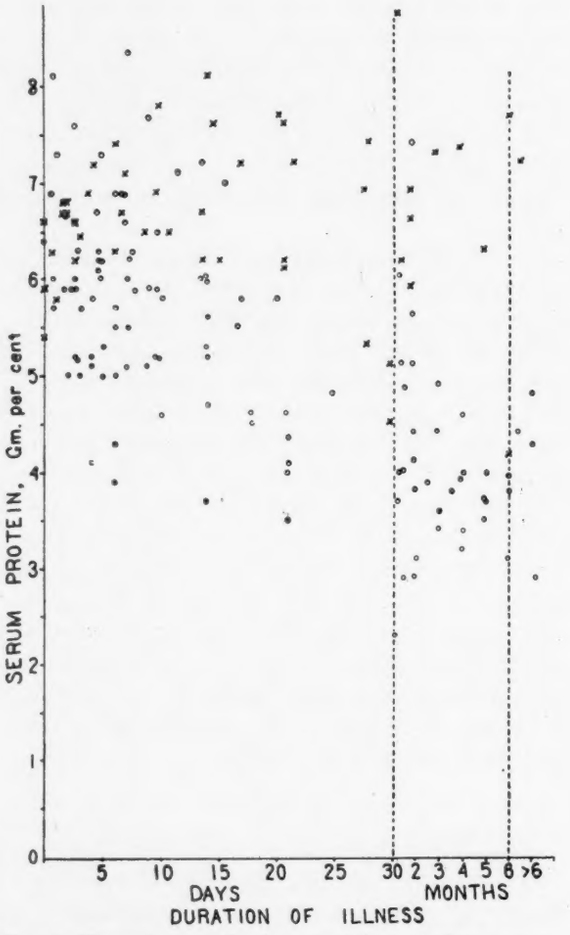

FIG. 3. The relation of serum proteins to edema; x = non-edematous patients; o = edematous patients.

weeks or more.[17] It will be noted that after the second month only patients with proteins below 5.0 per cent have edema. These are the patients with the nephrotic syndrome.* Edema was, in fact, found in all but two patients with serum proteins lower than 5.0 per cent at all stages of nephritis in this series. A large proportion of those with protein greatly reduced in the first few weeks belong to the group mentioned previously in whom the disease had been recognized only when it had all the characteristics of the nephrotic syndrome. In most of these, presumably it actually began much earlier. Since edema is practically universal in this series when serum protein is below 5.0 per cent, it is justifiable to infer that the deficiency of oncotic pressure resulting from this degree of hypoproteinemia is in acute nephritis of itself a sufficient explanation for edema. This does not signify that it is the sole cause for the edema since edema does not invariably appear in all states when serum protein falls below 5.0 per cent. Some of the factors operative in the production of edema at higher concentrations of protein may contribute to its production at these low levels as well. Their contribution at low concentrations, however, is so small that it is indistinguishable. In the early stages the incidence of edema diminishes as the concentration of protein increases. As the effect of hypoproteinemia diminishes other forces conducive to edema become less effective; or conversely, the tendency to edema increases as the oncotic pressure of the plasma falls. In seeking the other forces responsible for edema, therefore, the degree of associated deficiency of protein must be taken into consideration. Unfortunately, serum proteins were not measured in all cases and in an additional number of cases were not measured at the time when the edema was evaluated. Serum protein can be used as a point of reference, therefore, in only a fraction of the patients.

Of the patients for whom proteins are available, thirty had concentrations 7.0 per cent or higher. Seventeen were without edema. Of these, fourteen had no signs of heart failure; two had only electrocardiographic disorders; and one had an enlarged liver and a heart that appeared enlarged on x-ray. Thirteen patients had some degree of edema. Of these, five had frank evidences of heart failure and in four no signs of heart failure were discovered. The data on one of these patients were quite inadequate; the remaining three had had diuresis immediately. Another patient, with no evidence of heart failure except enlargement of the organ as judged by physical examination, reacted in the same manner. Although these four patients had edema at the time of observation, for purposes of this study they should be considered as non-edematous. The forces responsible for the production of edema were no longer active since diuresis was in progress. In another of the edematous patients the only evidence of cardiac disorder was an abnormal electrocardiogram but administration of digitalis was promptly followed by diuresis. In one, only enlargement of the liver and heart was noted but this patient had rheumatic heart disease. Analysis of the remaining subject was difficult because of the presence of pneumonia. In this group on the whole the correlation of edema with heart failure was extremely close.

Serum protein was 6.0 to 6.9 per cent inclusive in fifty-three patients, twenty-seven of whom had edema. Of the twenty-six without edema, twenty had no evidences of heart failure. Of the remaining six, one had a severe diarrhea that may have eliminated or prevented the appearance of edema; one had symptomatic relief from digitalis; one had an enlarged liver only; one had electrocardiographic changes; and two had enlarged hearts as judged on physical examination. Of the twenty-seven with edema, ten did not appear to have heart failure but of these, two died shortly afterward with obvious signs and postmortem evidence of heart failure; four had immediate diuresis. One subject had minimal edema and an enlarged liver at the time of the first observation; two days later when the edema had increased, frank heart failure developed. Of the edematous patients fifteen had undoubted heart failure; in four patients only enlargement of the heart was noted. In one subject the diagnosis of heart failure was not made until the venous pressure proved to be 165 mm. of water. The administration of digitalis elicited diuresis. Analysis of the remaining two subjects was complicated by the presence of emphysema and bilateral pulmonary tuberculosis, respectively. In this group the correlation between edema and heart failure is extremely close.

Serum proteins of 5.0 to 5.9 per cent were found in forty-six patients, thirty-eight of whom had edema. Among the eight without edema one had obvious heart failure with acute pericarditis; the other seven had no signs of heart

* Other patients with edema persisting so long do not appear because of the mode of selection of cases.

failure. Of the thirty-eight edematous patients twenty-four had unmistakable heart failure; two had only enlargement of the heart, one by physical examination, the other by x-ray as well; only in one were basilar rales heard, and in two there was dyspnea. Two patients had pneumonia which was accompanied with a fatal pneumococcus septicemia in one. Among the seven in whom no evidence of heart failure was found three had immediate diuresis; one had only puffiness of the face but shortly more extensive edema developed, with frank heart failure; one had a serum albumin of only 0.30 per cent and therefore belonged in the nephrotic group; one was suspected of rheumatic fever. In only one—or possibly two—of the series with proteins between 5.0 and 6.0 per cent, therefore, was it impossible to attribute edema either to heart failure or to extreme hypoalbuminemia.

Of the fifty-six patients with proteins lower than 5.0 per cent only two were free from edema. No evidences of heart failure were detected in twenty-eight of the fifty-four patients with edema; eleven had frank failure; nine had enlarged hearts by physical examination, x-ray, or both, one with pulmonary congestion by x-ray as well; five had basilar rales, accompanied with dyspnea in one. Such low concentrations can of themselves give rise to edema. Nevertheless, the predisposition to circulatory failure is manifest in this group and must have contributed to the incidence and severity of their edema.

Dyspnea. It was possible to evaluate dyspnea in 278 of the records. As criteria of this symptom histories and observations of the examining physicians were given greatest weight. It was disappointing to discover how little attention had been given to this important symptom, especially in earlier cases. In recent years it has been a subject of more careful inquiry. It was therefore necessary in some cases to rely upon records of respiratory rate. A rate of twenty-four or greater was accepted as evidence of dyspnea in adults and in young children a rate of thirty-two or more. Of the 278 patients, 163 had edema; of these, 75 had dyspnea which in twenty-eight patients was accompanied with orthopnea. The relative infrequency of orthopnea in heart failure of acute nephritis has been remarked upon before.[6] This may be one reason for the greater frequency of edema of the face and upper extremities. Sixty-two of the edematous patients with dyspnea, including all those with orthopnea, had outspoken signs of heart failure. Evaluation was complicated in five cases by the presence of pulmonary complications: one had bilateral pulmonary tuberculosis, one had pneumonia, the other three had pneumonia with septicemia. Although the remaining eight did not present frank signs of heart failure, all had some evidences of circulatory disorder, usually cardiac enlargement, basilar rales, or both.

Edema without dyspnea was noted in eighty-eight patients. The data for seven of these were for various reasons too scanty to warrant evaluation of the cardiac status. Thirty-five patients of this group had the nephrotic syndrome; ten had immediate diuresis (two of these had basilar rales which were accompanied with pleural effusion in one); the edema in four patients was purely allergic in character; one patient had only 6 gm. per cent of hemoglobin. Eight patients with minimal edema at the first observation without obvious evidence of failure developed progressive signs of failure as the edema increased. The slight initial edema may have denoted the beginning of cardiac decompensation in these cases. Outspoken signs of failure were discovered in six cases. The absence of evident dyspnea in these patients is puzzling, although attention has been called by others to this peculiar paradox.[6] One of these patients had an abnormal electrocardiogram, an enlarged heart on x-ray and a venous pressure of 205 mm. H_2O; two of them had venous pressures of 210 and 165 mm. of water respectively, the former with a circulation time of nineteen seconds; another had pulmonary congestion by x-ray, together with an abnormal electrocardiogram. These are illustrative of the reasons for the diagnosis of heart failure in the six cases. Four patients had more than one sign of heart failure, usually cardiac enlargement and rales; one of these patients had a serum albumin of only 2.4 per cent. Five had enlarged hearts only. One, whose record is quite incomplete, was given digitalis under the impression that he had cardiac insufficiency. There were seven desperately ill patients: four had septicemia, one had pneumonia, the remaining two died after short intervals with frank evidences of heart failure, verified at postmortem examination. In only twelve of the eighty-one, the seven with grossly inadequate data being omitted, was it impossible to demonstrate either some evidence of cardiac disorder or other sufficient causes for edema. In view of experiences with the other

cases signs of heart failure might have been discovered in some of these twelve by more assiduous examination.

Of the 107 patients without edema, only seven had dyspnea, accounted for in every case by pulmonary disease: asthma, bronchiectasis, pulmonary fibrosis or pneumonia. Of the 100 without edema or dyspnea, one had an enlarged heart on physical examination, another a venous pressure of 150 mm. of water. Puffiness of the face and an enlarged heart developed in a third patient the day after the first observation when he had been free from edema.

An analysis of basilar rales has been made. Their correlation with edema is similar to that of dyspnea. It seems unnecessary to present this in detail since it is almost implicit in the analysis of dyspnea. Just as basilar rales are less frequent than dyspnea, pleural effusions are less frequent than basilar rales. Their correlation with heart failure is also less consistent since they occur commonly in nephrotic patients. If these cases are omitted, the incidence of effusions supports the general thesis that heart failure is an important influence in the genesis of edema.

X-rays of Chest. X-rays of the chests of ninety-seven patients were taken during the periods under consideration. Of these patients sixty-five had edema, thirty-two did not. Of those without edema thirty had no evidences of heart failure (enlargement of the heart, pulmonary congestion or edema), although five had pneumonia, one mild pulmonary fibrosis and another fibrotic tuberculosis. Both cardiac enlargement and congestion of the lungs were found in one patient and cardiac enlargement alone in another. Among the sixty-five edematous patients twenty-eight had both cardiac enlargement and pulmonary congestion; ten had large hearts, in one accompanied with pneumonia; three had congestion and two pleural effusions. One of this last pair, despite the absence of cardiac enlargement or pulmonary congestion, had a venous pressure of 210 mm. of water. Of the twenty-two without x-ray evidence of heart failure twelve had the nephrotic syndrome, two had immediate diuresis, one had a venous pressure of 165 mm. of water and one had a doubtful nephritis. Four patients had complicating pulmonary disease: two pneumonia and two bilateral tuberculosis. One patient, who has been mentioned before, had already been digitalized for signs interpreted as heart failure. In the remaining subject no symptoms nor signs of heart failure nor other causes for edema were found.

Effect of Digitalis. Digitalis was given to thirty-nine patients because they presented evidences of heart failure. In many instances the condition was so serious that it did not seem justifiable to delay the medication long enough to ascertain whether bed rest and diet alone would be effective. In nine patients immediate administration of digitalis was followed promptly by diuresis. In eleven instances, after a delay from three to eight days during which edema remained unchanged or increased, digitalis elicited diuresis. There was no response in nineteen cases. Of these, four patients were desperately ill and died after a short interval: one had pericarditis, another rheumatic heart disease, a third had pneumonia and two had the nephrotic syndrome. Two patients received inadequate doses. In five cases the effects of digitalis could not be evaluated because the patients were too ill or had left the hospital. In two instances neither signs of heart failure nor edema were immediately benefitted by digitalis but both later subsided simultaneously. The records of the effects of digitalis in these cases compare favorably with records of its action in other types of acute heart failure. A beneficial action with diuresis, especially after a control period at rest in bed with restricted salt, is strong evidence of heart failure; but in a certain proportion of patients, for reasons similar to those reported in this series, digitalis may be ineffectual or its effect may be delayed by associated disorders.

Venous Pressure and Circulation Time. Venous pressure was measured in twenty-three patients, with circulation time (decholin) in twenty. Recently these measurements have been made on all patients with edema as soon as possible after admission to the hospital. Most of the measurements are derived from these recent cases. Although the number of patients in this particular series is relatively small, therefore, so far as it goes it is fairly representative of the acute nephritics that enter the hospital and is not composed entirely of cases selected because they presented symptoms and signs of heart failure. Occasionally it was impossible to make the observations as early as might have been desired. The results are shown in Table 1. The first ten patients with venous pressures varying from 115 to 410 mm. had outspoken symptoms and signs of heart failure with corresponding changes

in chest x-rays (with the exception of Case B7928 who had no x-ray). Case C7112 probably belongs in the same class; but for some reason there are no remarks in his record about dyspnea or orthopnea. This patient had serum albumin low enough to put him in the nephrotic category. Case 98277 had all the symptoms and signs of heart failure, with a venous pressure of 240 mm., but x-ray revealed enlargement of the heart only. Case 96140, without symptoms or signs of failure other than a pleural effusion, had a venous pressure of 210 mm. and an enlarged heart on x-ray. Case A97724, without symptoms or signs and with a negative x-ray, had a venous pressure of 165 mm. As further evidence of heart failure both these patients responded to digitalis with diuresis. The absence of overt respiratory disorders in nephritics who have other evidences of heart failure was commented upon in the discussion of dyspnea. Several other observers have remarked that elevated venous pressure occurs more consistently than other evidences of heart failure in acute nephritis.[6,8,11] Case A20361, because of a pneumonia, was hard to evaluate. Case B3204 had the nephrotic syndrome. His heart was somewhat enlarged on x-ray and his venous pressure was 110 mm. The next six patients had venous pressures of 100 mm. of water or less. The first of them, Case B15552, with a venous pressure of 100 mm. and an enlarged heart by x-ray but no pulmonary signs nor symptoms, responded to digitalis with diuresis. The next two, Cases B95916 and A89606, were in phases of active diuresis when they were studied. The chest x-ray of the former was not taken until two days after the other observations. Case 62428 had questionable edema and rhonchi but no rales in her chest. Venous pres-

TABLE I

VENOUS PRESSURE AND CIRCULATION TIME IN ACUTE NEPHRITIS

Case	Edema	Venous Pressure (mm. H_2O)	Circulation Time (seconds)	X-ray*	Dyspnea†	Orthopnea†	Rales	Effusion	Action of Digitalis†	Remarks
B7928	+	285	–	–	+	+	+	±	–	
B11149	+	410	–	EC	+	+	+	0	–	
C20147	+	160	15	ECF	+	+	+	+	–	
B81051	+	120	20	EC	+	+	+	0	–	
A69232	+	140	25	EC	+	+	+	0	+	
42550	+	150	11	ECF	+	+	+	+	–	
B63225	+	250	20	EC	+	+	+	0	+	
36-86-34	+	120	14	EC	+	+	+	0	+	
A65693	+	115	14	EC	+	+	+	0	–	
C24145	+	120	13	CF	+	+	+	+	–	
C7112	+	190	20	ECF	–	–	+	+	–	Nephrotic
98277	+	240	–	E	+	+	+	0	0	
96140	+	210	19	EF	0	0	0	+	+	
A97724	+	165	15	0	0	0	0	0	+	
A20361	+	205	14	E	0	0	0	0	–	Pneumonia
B3204	+	110	13	E	0	0	0	0	–	Nephrotic
B15552	+	100	12	E	0	0	0	0	+	
B95916	+	85	12	0**	0	0	0	0	0	During diuresis
A89606	+	80	10	–	0	0	0	0	0	During diuresis
62428	?‡	90	10	0	0	0	?§	0	0	
C33766	0	85††	15††	EC	+	0	+	0	0	
C26564	+	50 to 100	14	0	+	0	0	0	–	Nephrotic
B78197	0	150	14	0	0	0	0	0	0	

* E = enlarged heart; C = pulmonary congestion; F = pleural effusion.
† + = positive; 0 = negative; – = no observation. (A positive effect of digitalis is diuresis.)
‡ Edema minimal.
§ Rhonchi, but no rales, heard.
** X-ray was taken 2 days later.
†† Measurements made 3 days later.

sure in Case C33766 was measured five days after the other observations. She had obvious heart failure, both by physical examination and x-ray. Case C26564 belonged in the nephrotic class. Finally Case B78197 had a venous pressure of 150 mm. without edema or evidence of heart failure. The patients with edema, therefore, consistently had high venous blood pressure with evidences of heart failure unless they had the nephrotic syndrome. The manifestations of heart failure did not, however, regularly follow the conventional pattern. One rather striking departure was the infrequency of prolonged circulation time. In spite of the high venous pressures, only three patients in the series had circulation times longer than fifteen seconds. This discrepancy has been remarked by other observers.[8,11]

COMMENTS

In this series of cases of acute glomerulonephritis which includes the majority of patients with this condition admitted to a large general hospital in the course of thirty years, the correlation of edema with the generally accepted clinical criteria of congestive heart failure is so close that it seems impossible to escape the conclusion that cardiac decompensation must play an important if not the most important role in the genesis of acute nephritic edema. To be sure the work lacks elegance since the investigation has not been systematically conducted with the direct objective of evaluating cardiac function in all cases from the beginning of the study. The present evaluation is a retrospective assessment of the cumulative impacts that have compelled us to direct our attention more and more to the function of the heart in the production of acute nephritic edema. In retrospect recognition of the facts was unduly tardy; but tradition, preconceptions, hypotheses and faulty observations had their usual obstructive influences.

Although serum albumin deficits may become so great that they can of themselves cause edema, deficits of this degree are seldom encountered in the early stages of acute nephritis. Moderate deficits do occur as they do in most other acute diseases. These may be only examples of the general reaction to injury.[18,19] They undoubtedly contribute to the formation of edema but are too paltry to be important factors. Anemia may sometimes contribute to a lesser degree.[20] Some early analyses of edema fluids and transudates from patients with acute glomerulonephritis revealed unusually high concentrations of proteins in these fluids, giving rise to the impression that the permeability of the capillaries in this condition was increased.[17] The accumulation of more data of greater precision has dispelled this impression. The concentration of proteins in acute nephritic transudates appears to be extremely low.[21] It is possible that in individual instances local inflammatory reactions, not uncommon in the disease, may provoke exudates containing higher concentrations of protein. It is not unusual in acute nephritis to find localized swellings suggesting angioneurotic edema. Patients with this disease seem to have a predisposition to allergic reactions or vascular reactions that follow allergic patterns. Some reactions of this type were noted in this series. Urticarial and angioneurotic transudates do contain relatively high concentrations of protein.[22,23] Such reactions appear to be attended by increased permeability of the local vessels. However, the general edema of nephritis does not have the characteristics of angioneurotic edema.

The edema of acute nephritis, like that of heart failure, has been attributed to reduction of renal plasma flow and glomerular filtration. These disorders are undoubtedly common in acute nephritis but are not invariable nor are they closely correlated with the presence or absence of edema. Few clearances were measured in this series but there is no correlation between the incidence of edema and azotemia, which must be roughly correlated with glomerular filtration. In acute nephritis, as in heart failure, a satisfactory explanation of edema must be generally applicable. The demonstration that glomerular filtration is reduced in the majority of nephritics with edema has no bearing on the incidence of edema in the minority. Moreover, it is hardly conceivable that reduction of glomerular filtration could so profoundly affect the excretion of salt and water without disturbing the excretion of nitrogen. The urine in acute nephritis may be fairly highly concentrated, and nitrogen elimination may be well preserved, while the concentrations of sodium and chloride in the urine are almost negligible. Indeed it resembles in many respects the urine of patients with heart failure. The most consistent functional disorder is the failure to excrete sodium chloride which must be attributed to reabsorption of salt by the tubules.

Oliguria may become extreme; occasionally there is complete anuria. Such episodes are usually associated with profound circulatory disturbances and may indicate the presence of a state comparable to that of "acute renal failure." Peculiar dissociations of function have been reported, especially the presence of azotemia with normal phenolsulfonphthalein excretion and reduction of urea clearances out of proportion to clearances of creatinine.[12,23–26] Frequent examples of the former discrepancy were found in this series. When urine is excreted by patients with "acute renal failure," however, it is not deficient of sodium, like that of acute nephritis. In "acute renal failure" reabsorption of sodium is impaired, presumably because the tubules are injured.

In the last analysis reduction of glomerular filtration and tubular damage with back filtration could account for the oliguria of acute nephritis but would not account for edema. Even complete anuria does not lead to spontaneous edema Patients or animals with this condition drink only enough to replace fluids lost through extrarenal channels. Edema occurs only if excessive amounts of fluid are given parenterally or if the equilibrium that controls exchanges of fluid between blood and the perivascular fluids is so disturbed as to favor transudation. This subject has been discussed at some length in a recent analysis of the origin of cardiac edema,[27] to which the edema of acute nephritis is quite analogous. In neither condition can the role of thirst be ignored. In their behavior towards sodium salts and water patients with acute nephritis resemble those with heart failure. Concentrations of sodium and chloride in the urine are minimal and do not increase when salt is given. Instead, sodium chloride is retained, together with water, so that edema increases. Water without salt is usually better excreted. In fact, except in conditions of extreme oliguria, an equilibrium can usually be reached in which, at a constant low salt intake, water is usually excreted freely. If there is anuria or extreme oliguria, thirst usually fails or ingestion of fluid provokes vomiting, as it does in the presence of anuria from other causes. On the whole, the concentrations of sodium in the serum in acute nephritis are not greatly disturbed. Of twenty-two measurements made at the time of evaluation of the present series of cases seventeen fell in the range 132 to 141 mEq./L. Of the remainder, two from patients with edema and obvious heart failure were 145 and 149 mEq./L.; and two from patients with the nephrotic syndrome, in one accompanied with heart failure were 127 mEq./L. In spite of the priority of sodium salts in the production of edema in acute nephritis, as in heart failure, sodium in the serum tends to be more often reduced than elevated, indicating that water is retained somewhat in excess of salt. The same tendency is evident in the combined concentrations of bicarbonate plus chloride in Figure 4.

With respect to the relative proportions of bicarbonate and chloride in the serum, the two conditions are somewhat different. (Fig. 4.) Of 110 measurements of bicarbonate in acute nephritis only one was as high as 30 mEq/L. This may signify that respiratory embarrassment is a less serious element in acute nephritis. Bicarbonate tended to be somewhat higher in the patients with edema and heart failure than in those without edema. Greatly reduced values were found chiefly in persons with grossly elevated non-protein nitrogen and were probably referable to salt wastage and accumulation of other anions. In a large proportion of the patients, especially those with edema, chloride was abnormally high, a phenomenon that has been noted before. There appears to be a predilection to reabsorb more chloride or sodium chloride then bicarbonate. From the combined concentrations of chloride and bicarbonate it is evident that there is some reciprocal relation between chloride and bicarbonate but this does not appear to be complete, since elevation of chloride is greater and more frequent than depression of bicarbonate and concentrations of bicarbonate plus chloride are frequently in or above the high normal range. These disorders cannot be correlated with either edema or heart failure directly and are not consistently observed. They represent nothing more than a statistical tendency to a disturbance of acid-base equilibrium with a particular pattern. They merit investigation but seem to have no bearing on the present subject.

The pattern of heart failure in acute nephritis may have all the characteristic features of congestive failure from primary cardiac disease but differs frequently in certain respects from the latter. These differences involve the relative weight rather than the general nature of the disorders in the two conditions. Although dyspnea and pulmonary congestion are commoner

than most descriptions of acute nephritis indicate, they are not so prominent in this condition as they are in other types of congestive failure; orthopnea is relatively inconspicuous. Prolongation of the circulation time is infrequent and inconsiderable. On the other hand, venous pressure is quite consistently increased. In some of the patients it reached heights that had been quite unsuspected and seemed out of proportion to other symptoms and signs of heart failure. These distinctive features have some bearing on the peculiar distribution of the edema, its tendency to disregard the effects of gravity, illustrated by its diffuse distribution and greater predilection for the face. The possible role of local circulatory disturbances cannot, however, be excluded.

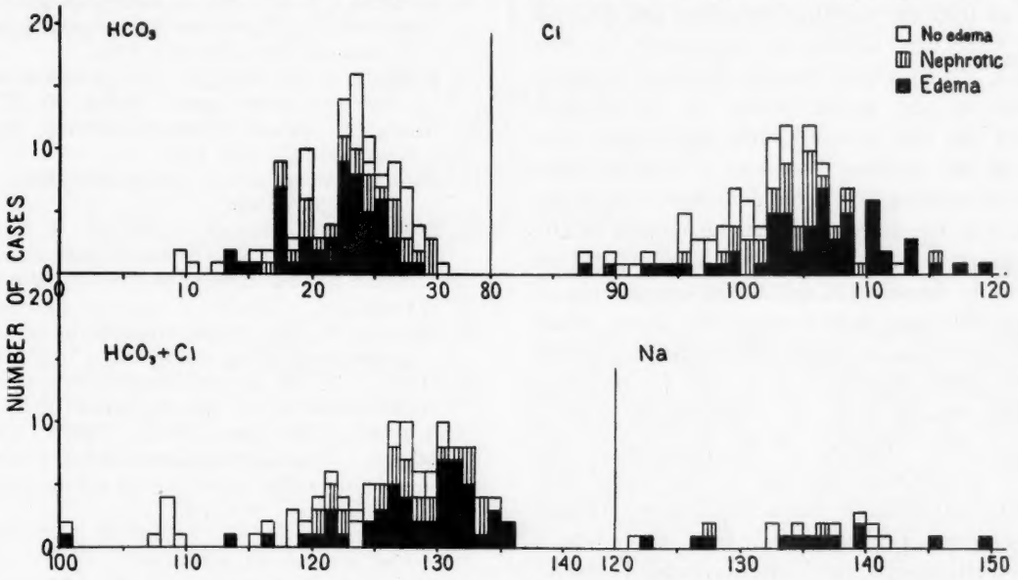

FIG. 4. The relation of serum electrolytes to edema. All nephrotic patients were edematous.

Although the onus for the production of edema can not be placed directly upon failure to excrete sodium (or rather, excessive reabsorption of sodium), administration of sodium salts exaggerates the edema just as it does in other types of congestive failure. In addition it appears to aggravate symptoms and signs of failure. In this respect it is reputedly more deleterious in acute nephritis than it is in simple heart failure. In other edematous states, for example, nephrosis, accumulation of edema of far greater degree may cause no evident circulatory disturbances. In conditions of hypoalbuminemia, however, the circulation is essentially intact. Moreover, there is in such states no pulmonary congestion nor consequent tendency to transudation in the lungs. For the purposes of this argument the distinction between acute nephritic and hypoproteinemic subjects with respect to their responses to salt is less important than the similarity of acute nephritic and cardiac subjects. The reason for the differences in detail between the reactions of simple cardiac and acute nephritic subjects are more likely to be discovered if the role of heart failure in the production of acute nephritic edema is established and recognized.

Although edema and heart failure in acute nephritis are usually associated with hypertension, the correlation, as Figure 3 shows, is not consistent enough to warrant the conclusion that hypertension is the cause of failure. There is a similar lack of correlation with the severity or outcome of the disease. Odel and Tinney[7] failed to establish any relation between heart failure and either hypertension or the severity of the disease. Master, Jaffe and Dack[3] found electrocardiographic disorders which they interpreted as significant in nineteen of twenty-four patients with acute nephritis. This led them to conclude that the disease directly injured the myocardium, a view that is shared by certain others on the same or more general grounds.[4,5] In our own series electrocardiographic abnormalities were frequent but often comparatively trivial. This series, like others,[5] bears out Volhard's[1] statement, quoted in the introduction: " . . . almost every case that dies in the acute stage of the disease dies of cardiac insufficiency. . . . " Moreover, in the majority of fatal cases obvious signs of myocardial injury,

usually inflammatory in nature, were found postmortem. The majority of these fatal cases, however, had serious septic complications. Death and the cardiac lesions could be attributed as much to the underlying disease as to the nephritic reaction. Rubin and Rapoport[5] have suggested that the cardiac disorders are derived chiefly from the infection responsible for the nephritis. Postmortem examinations of patients who die in the acute phase of the disease therefore do not throw much light upon the nature of the cardiac disorders of subjects who recover or succumb to later consequences of the disease. For the same reasons the nature of the renal lesions are not revealed by similar studies. It can only be elucidated by examinations of patients who succumb during the acute phase to some accident or intercurrent disease which does not affect the kidneys, or else by biopsies, until the disease can be reproduced experimentally. The disorder of the kidneys in the majority of patients appears to be completely reparable and to have characteristics resembling a highly specific type of allergic reaction in which the glomerulus is particularly involved. It would be impossible to deny that other parts of the vascular system, including the heart, participated in this reaction.

SUMMARY

The incidence and origin of edema in the acute phase of glomerular nephritis has been examined by an analysis of clinical symptoms and signs and special examinations of 291 patients admitted to the New Haven Hospital in a period of about thirty years. This analysis indicates that the chief disorder responsible for edema in acute glomerulonephritis is congestive heart failure.

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Seminars on Blood Coagulation

Differential Diagnosis, Pathogenesis and Treatment of the Thrombocytopenic Purpuras*

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SPLENECTOMY has been performed with varying success in literally thousands of patients with "idiopathic" thrombocytopenic purpura since Kaznelson first suggested this operative procedure thirty-seven years ago.[1] Bone marrow aspiration, first proposed by Arinkin twenty-four years ago,[2] has been of considerable aid in differentiating the various types of thrombocytopenic purpura. Nevertheless, at the present time the role of the spleen in these conditions is not well understood[3] nor is the appearance of the bone marrow of unequivocal help in differentiating the "idiopathic" variety from the "toxic"[4] or "infectious"[5] or "allergic" varieties, or even from the "splenomegalic"[6] variety. Examination of the bone marrow has really been of less help in predicting the results of splenectomy in idiopathic thrombocytopenia than in averting splenectomy in those patients with leukemia, aplastic anemia, pernicious anemia, chronic hypochromic anemia, lymphomatosis, carcinomatosis, osteosclerosis and tuberculosis.[7,8] It is this group of patients, frequently said to have "secondary" or "symptomatic" thrombocytopenic purpura, who almost certainly will receive no benefit from splenectomy and may in fact derive irreparable harm from this procedure, that one must be most anxious to segregate from the other varieties.

It is the purpose of this presentation, therefore, to review the differential diagnosis of the thrombocytopenic purpuras and to attempt to correlate some of the more recent information concerning the pathogenesis and treatment of these conditions, particularly the idiopathic variety.

DIFFERENTIAL DIAGNOSIS

Thrombocytopenic purpura has been observed in a large variety of clinical states, infectious,[5] toxic,[4] allergic,[9] neoplastic, granulomatous and so forth. It has been a feature of such hematologic conditions as pernicious anemia, hypochromic anemia, aplastic anemia and leukemia. In many such patients the purpuric manifestations may be rather mild or the thrombocytopenia of such a low order of magnitude as to cause no clinical manifestations. In some, however, the hemorrhagic tendency and the thrombocytopenia may be so severe as to constitute the presenting aspect of the underlying disorder.

A complete medical work-up is indispensable in any patient suspected of thrombocytopenia. Special emphasis in the history must be placed upon drug ingestion, accidental or occupational exposure to heavy metals, aromatic chemicals or irradiation. Interest should be manifest in the relationship of the hemorrhagic tendency to any changes in the external environment that might suggest hypersensitivity.[9] Attention should be paid to a possible correlation with the menstrual cycle.[10,11] Diligent search should be made for evidences of a systemic illness of which the purpura is just one manifestation. The existence of an acute or chronic infection must always be suspected.[5] In the former category are infectious mononucleosis, scarlet fever, measles, rubella and several others; in the latter are tuberculosis and subacute bacterial endocarditis. In the physical examination special search must be made for significant lymphadenopathy and splenomegaly

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as these findings, particularly the latter, are extremely uncommon in "idiopathic" thrombocytopenic purpura.[6]

The laboratory examination of these patients should include a careful study of the peripheral blood and of the bone marrow. As to the former, the finding of a macrocytic anemia should raise the suspicion of pernicious anemia. The finding of a microcytic hypochromic anemia leads to a consideration of the question as to whether the thrombocytopenia is secondary to erythroid hyperplasia of the marrow and mechanical displacement of the megakaryocytes (analogous to the situation in pernicious anemia) or whether the anemia is secondary to blood loss, for example, menorrhagia, occurring as a result of the thrombocytopenia. In the former state of affairs the thrombocytopenia and hemorrhagic diathesis are usually mild and a trial of iron therapy will usually resolve the diagnostic problem. The occurrence of either significant leukopenia or leukocytosis militates against the diagnosis of "idiopathic thrombocytopenic purpura" and search should be undertaken for the causes of these abnormalities in the white cells. As for the thrombocytopenia itself, it is a common laboratory observation that both indirect estimation of the number of platelets by examination of either the ordinary blood smear or one prepared by Dameshek's method[12] and direct count of the platelets by a modification of the Rees and Ecker[13] technic are associated with technical variability of greater magnitude than is desirable in clinical laboratory procedures. We have preferred the Pohle[11] modification of the latter technic. The Brecher and Cronkit[14] modification using phase microscopy offers definite hope for increasing the validity of platelet counting. Clot retraction, of course, carries a high correlation with platelet counts and may be found very helpful whenever there is reason to doubt the accuracy of the platelet counts.[15] It is in a similar connection that we have found studies of prothrombin conversion most useful.

To digress for a moment, the venous coagulation time in patients with thrombocytopenia is almost invariably within normal limits. Until recently, therefore, it had been assumed that there was little or no disturbance in blood coagulation in this condition other than the production of a soft non-retractile clot. Quick and associates,[16] however, have clearly demonstrated that there is much slower conversion of prothrombin to thrombin in the absence of platelets than in their presence. The rate of prothrombin conversion is, within certain limits, proportionate to the number of platelets. Expressed in another way, in thrombocytopenia the prothrombin time of serum is almost the same as the prothrombin time of plasma, indicating that their prothrombin content is the same and that essentially no prothrombin is consumed during the initial stages of coagulation. On the other hand, in blood with normal platelets the prothrombin time of the serum produced is much higher than the prothrombin time of the original plasma, indicating that the prothrombin content of the serum is lower and that most of the available prothrombin was converted to thrombin during the process of coagulation.

In most patients with severe thrombocytopenia the bleeding time is prolonged and the capillary fragility is increased. The latter may be studied either by means of a suction test[17,18] or by the more conventional tourniquet test. Because of the almost universal availability of a sphygmomanometer, we have preferred the latter technic. We apply the standard cuff at 100 mm. Hg pressure (if the systolic pressure is lower than 100 mm. Hg we use 10 mm. below the systolic pressure) to the upper arm for ten minutes. After the plethora of the arm has been dissipated, the number of petechiae in a 2.5 cm. circle (the upper edge of which is 4 cm. distal to the antecubital crease) on the flexor surface of the forearm is counted. Most normal individuals will have fewer than 10 petechiae. Between 10 and 20 petechiae represents a borderline situation and more than 20 petechiae is indicative of a significant increase in capillary fragility. It must be pointed out here that both increased bleeding time and increased capillary fragility are present in the non-thrombocytopenic purpuras and neither of these tests therefore can be used to differentiate the thrombocytopenic from the non-thrombocytopenic varieties.

It is now universally accepted that examination of the bone marrow elements is indispensable in the differential diagnosis of the thrombocytopenic purpuras. Since formal marrow trephine biopsy is not without significant hazard in patients with hemorrhagic tendencies, it has become the more usual practice to perform a bone marrow aspiration. This procedure is essentially without risk when performed properly either in the sternum, iliac crest, spinous process or in the tibia of an infant. It yields invaluable

information in the diagnosis of leukemia, pernicious anemia in relapse and myeloma and may be very helpful in the diagnosis of aplasia, osteosclerosis, lymphomatosis and carcinomatosis. There is definite difference of opinion with regard to the diagnostic and prognostic significance of the marrow morphology in idiopathic thrombocytopenic purpura.[7,8,19] Although most observers agree that in many patients with idiopathic purpura the number of megakaryocytes is increased and that there is a tendency to immaturity, degeneration and lack of platelet formation, some observers believe that the variability of normal marrow appearance, the similar appearance of the marrow in toxic,[4] infectious[5] and splenomegalic[6] thrombocytopenia, and the numerous exceptions to the characteristic findings in idiopathic thrombocyto penia make it impossible to make a definite diagnosis of idiopathic thrombocytopenic purpura on the basis of marrow examination alone. An excellent review of this very problem was presented recently by Presley, Best and Limarzi.[8] Because idiopathic thrombocytopenic purpura so often occurs in adolescent and young adult females, because acute disseminated lupus erythematosus occurs most frequently in this same sex and age group, and because thrombocytopenia is a frequent finding in disseminated lupus, we have made it a practice to search for "L.E." cells in all our recent patients with thrombocytopenia.

The rare disorder "thrombotic thrombocytopenic purpura"[20] characterized by widespread capillary thrombi is not clearly related to the other forms of thrombocytopenia and will not be discussed in this paper.

PATHOGENESIS

Most hematologists are agreed that mechanical displacement of the megakaryocytes is the chief reason for thrombocytopenia in leukemia, pernicious anemia, hypochromic anemia, aplastic anemia and in the majority of patients with disseminated carcinomatosis, tuberculosis, lymphomatosis and granulomatosis (e.g., sarcoidosis). In some patients in the latter group, however, there is splenomegaly and whenever this condition is present the possibility exists that abnormal function of the spleen is responsible for the thrombocytopenia. This situation also obtains in portal or splenic vein hypertension with or without cirrhosis of the liver, and in Gaucher's disease and Felty's syndrome. When thrombocytopenia seems to be the result of splenomegaly, the megakaryocytes are usually present in normal or increased numbers in the marrow and the pathogenesis may not be unlike that which is prevalent in some cases of idiopathic thrombocytopenia.[6]

As mentioned in the introductory paragraph of this paper, the role of the spleen in the pathogenesis of idiopathic thrombocytopenic purpura is incompletely understood. The chief difficulties in assessing the importance of the spleen in this disease are that a significant fraction of patients, particularly children, have a spontaneous and permanent remission without splenectomy[21] and that a significant fraction of patients who are splenectomized do not undergo remission.[22,23] Thus the presence of the spleen is not always detrimental in these patients nor is the absence of the spleen always of benefit. Despite this apparent contradiction the fact that splenectomy does frequently produce remission focussed the attention of most hematologists on abnormalities of splenic function.

There were two major schools of thought. Frank[24] in 1915 suggested that the spleen inhibited the formation of platelets from megakaryocytes. This hypothesis is supported by Dameshek and Miller[25] and by studies which showed that a splenic extract[26] could cause thrombocytopenia in animals; however, there is some controversy about these latter studies.[27,28] The other school of thought[1,29,30] postulated that the spleen was actually destroying the platelets at an increased rate. Neither school explained satisfactorily the occurrence of spontaneous remissions or the frequent ineffectiveness of splenectomy. The most recent studies in this disorder have tended to point away from the all-importance of the spleen in the pathogenesis of the disease and have favored the existence of a humoral substance, probably an antibody in the plasma. Such a humoral substance was postulated by Epstein and co-workers[31] who observed seven pregnancies occurring in five mothers with thrombocytopenia, three of whom had been previously splenectomized. All of five children born to the splenectomized mothers were thrombocytopenic at birth but underwent a spontaneous remission within a few weeks. One of two children born to the non-splenectomized mothers had a similar transient thrombocytopenia. A study was then undertaken of the literature concerning other pregnancies occurring in thrombocytopenic females and it became evident that whether or not the mother still

possessed her spleen at the time of delivery the large majority of infants had thrombocytopenia at birth. It was concluded that some "humoral substance," independent of the presence or absence of the spleen, was transferred across the placenta into the circulation of the fetus, producing thrombocytopenia. At first it was thought that such a substance might be an estrogenic hormone because of the well known observation that idiopathic thrombocytopenic purpura in adults is almost exclusively a disease of females.[32] Moreover, thrombocytopenic purpura had been observed in a few patients following large doses of estrogen.[33] However, more recent studies have led to the hypothesis that this substance may well be an antibody and in fact a platelet agglutinin. Such an agglutinin has been described in patients with sedormid[34] or quinidine[35] thrombocytopenia.[36] Evans and his associates[37] were probably the first, however, to demonstrate a platelet agglutinating factor in the serum of some patients with idiopathic thrombocytopenia. This group of workers gave considerable impetus to the immunologic concept of this disease when they called attention to the occasional co-existence of acquired hemolytic anemia and thrombocytopenic purpura and to the presence of a positive anti-globulin (Coombs) test in some patients with idiopathic thrombocytopenia without anemia. At just about this time Harrington and his coworkers[38] were observing that the transfusion of blood or plasma from most patients with idiopathic thrombocytopenia into normal non-thrombocytopenic subjects promptly decreased the platelet counts of the recipients, the thrombocytopenic effect persisting for from five to seven days. Some of their patients retained the thrombocytopenic factor in their plasma after their spleens had been removed and even after the splenectomized patients' platelet counts had returned to normal. It is also of interest that one of the recipients showing a thrombocytopenic effect had previously had his spleen removed. Several recent studies have been reported on the survival of platelets transfused into patients with thrombocytopenia.[39,40] Both platelet-rich blood and suspensions of platelets[41] have been used. Platelet disappearance is extraordinarily rapid when the recipient has "acute idiopathic thrombocytopenic purpura." However, when the recipient has either the more chronic form of this disease or thrombocytopenia associated with leukemia or aplastic anemia, platelet survival time may be significantly longer. These results have been interpreted to indicate that when the platelet survival time in the recipient is short, the recipient's thrombocytopenia is probably due to an increased rate of destruction of platelets. However, when the survival time in the recipient is long, decreased production of platelets may be the chief mechanism involved in the pathogenesis of his thrombocytopenia. Stefanini and his co-workers have recently studied rather extensively one patient with chronic idiopathic thrombocytopenic purpura.[42] This patient had a high titer of platelet agglutinins. Platelets injected into this patient disappeared rapidly. When this patient's plasma was injected into normal recipients, the latter developed thrombocytopenia, purpura and degenerative changes in the megakaryocytes. The platelet agglutinin could be detected in the recipients' serum for twelve to fourteen days. Although this patient was moderately improved by splenectomy, she continued to show thrombocytopenia and the thrombocytopenic factor in her plasma persisted. Her plasma also showed a thrombocytopenic effect in splenectomized recipients which, however, appeared to be of shorter duration than that in normal recipients. Stefanini therefore concluded that in this one patient the thrombocytopenia was most probably due to the effects of the circulating agglutinin on the platelets and possibly on the megakaryocytes. The observations on splenectomized recipients also indicated that the spleen may be responsible for the removal of "sensitized" platelets inasmuch as the recipients who retained their spleens showed a more pronounced and prolonged thrombocytopenic effect following injection of the patient's plasma than those who had their spleens removed.

Harrington's most recent studies concern the existence of platelet types similar to blood groups.[43] He believes that at least three types may exist. In this regard he believes that there are two types of neonatal thrombocytopenia. One is the result of transmission across the placenta of maternal platelet auto-agglutinins in instances in which the mother has had thrombocytopenia and the baby then has transient thrombocytopenia which remits within a few weeks. He also believes that there is another type of neonatal thrombocytopenia in which the mother has developed an iso-agglutinin for the baby's platelets in a manner similar to Rh iso-immunization. In these instances the

mother does not have thrombocytopenia but the babies have transient thrombocytopenia which improves rapidly usually within a few days.

The thrombocytopenic factor in the plasma of patients with idiopathic thrombocytopenic purpura has also recently been studied by Wilson and co-workers[44] who did platelet counts on the recipients, both by the indirect and direct methods. Harrington originally had used the indirect method. These observers found that when the direct method was used no thrombocytopenic effect could be demonstrated in the recipients, in contrast to the thrombocytopenia found when the indirect method was used. They concluded that the thrombocytopenic factor might be diluted out by the direct platelet counting method. Thus far, these observations have not been confirmed.

In connection with the observations on platelet transfusions, it has recently been observed that the survival time of transfused platelets into either normal or thrombocytopenic recipients becomes progressively decreased with repeated transfusion.[40,45] This seems usually to be due to the development of a platelet iso-agglutinin. These observations suggest that the therapeutic usefulness of platelet transfusions in thrombocytopenic patients may be limited.

As already mentioned, increased capillary fragility is one of the usual accompaniments of thrombocytopenia. The pathogenesis of this increased fragility is about as obscure as that of the thrombocytopenia.[46] It has already been mentioned that increased vascular fragility may occur without thrombocytopenia. Thrombocytopenia may also occur without increased vascular fragility. Bedson's observations are of interest in this connection.[47] He has shown that injection of an agar-serum in animals produces thrombocytopenia without purpura. However, when such an injection is preceded by an injection of anti-red cell serum both thrombocytopenia and purpura result. Macfarlane[46] called attention to the fact that splenectomy may improve capillary fragility without altering the number of platelets. Robson[48] pursued these observations and concluded that the vascular defect in purpura was improved almost immediately by splenectomy, long before any increase in platelets could be observed. In fact, before the advent of adrenal steroids he[48] ventured the theory that these changes in vascular fragility might be a non-specific effect of operative interference. With the availability of cortisone and corticotropin Robson[18] was able to show that adrenocortical activity was related to capillary resistance. Faloon and co-workers[49] confirmed these observations and showed that the administration of such hormones regularly improved the vascular fragility in thrombocytopenic purpura, regardless of etiology, but only irregularly increased the platelet count and then only after several days following the improvement in capillary fragility.

Certain speculations concerning the role of the spleen in the pathogenesis of idiopathic thrombocytopenic purpura are now in order. In any given patient one or more of these abnormalities of function may be operative. The spleen may be the site of formation of platelet agglutinins. In some patients it may be the major or only source of these antibodies. In other patients the titer of agglutinins and the thrombocytopenic effect of the plasma will be unchanged by splenectomy. The spleen may be concerned with the removal of "sensitized" platelets from the circulation. In this respect it may perform much the same function in regard to platelets as with spherocytic red cells in some patients with hemolytic anemia. There is also a possibility that the spleen secretes a substance which interferes with the maturation of megakaryocytes and the release of platelets from the marrow. Finally, the spleen may be directly or indirectly concerned with capillary fragility. It is probable that either the platelets or the adrenal cortex also are concerned in this function.

TREATMENT

It is obvious from the many factors that may be concerned in the production of thrombocytopenic purpura that the differential diagnosis in these conditions bears a vital relationship to the plan of therapy. If an infection appears to be present or if drugs or allergens appear to be implicated, conservative management is in order. If there is evidence of mechanical displacement of the megakaryocytes in the bone marrow, the primary condition responsible for this displacement should be treated by whatever means are available. If there is splenomegaly, the likelihood of the patient having idiopathic thrombocytopenic purpura is minimal. However, in those situations in which megakaryocytes are present in the marrow and in which the thrombocytopenia

appears to threaten the survival of the patient, splenectomy may be considered. Ehrlich and Schwartz[6] have obtained encouraging results with splenectomy in some patients with splenomegalic purpura. If the primary disease in the spleen, however, is leukemia or lymphoma, the transient beneficial effects of splenectomy will soon be overshadowed by the malignant nature of the original disease.

The present day therapy of "idiopathic thrombocytopenic purpura" may be conservative, but may also include the use of corticotropic or adrenocortical hormones, the use of transfusions particularly of platelet-rich polycythemic blood with siliconized apparatus and, finally, the use of splenectomy.

The age of patients presents an important factor in deciding upon the course of treatment. The majority of children show a marked tendency to spontaneous and complete recovery.[21] It is therefore believed by most observers that splenectomy in childhood should be reserved for uncontrollable bleeding or for very chronic or recurrent purpura. In such patients, however, splenectomy has a significant proportion of failures.[21] It may be wise therefore to employ hormonal therapy in these children in addition to the usually employed expectant management. In adults there is also a tendency to spontaneous remission but most series indicate that this occurs much less commonly than in children.[22,23] In adults also the menace of a cerebral vascular accident is much greater than in children. Nevertheless, most hematologists believe that a trial of at least a few months of conservative management is desirable in the majority of patients. During this interval if the hemorrhagic tendency is severe, transfusions may be employed but perhaps of greater help is the use of ACTH and cortisone. There have now been several series of patients treated with these hormones.[18,49–54] All of the observers have reported some success but the completeness and permanence of the success has not been constant. It is now generally agreed that, as in most other clinical situations, these hormones have their greatest usefulness in temporary emergencies and as help in expectant management. Thus in idiopathic thrombocytopenic purpura we have found ACTH and cortisone most helpful in the management of fulminating hemorrhage, particularly menorrhagia, and in the preoperative preparation of patients for splenectomy. Inasmuch as the capillary fragility is improved and a remission of the thrombocytopenia may be obtained, the operative mortality may well be decreased as a result of this preparation. It has usually been our policy to begin tapering off the dosage within a day or two after splenectomy. Supplementary potassium and sodium restriction have been used in all patients during hormonal therapy. In our own series we have had the clinical impression that ACTH has been more successful than cortisone but this may be a matter of dosage. No difficulties in wound healing have been encountered. We have also had some success with these hormones in the hemorrhagic emergencies resulting from the thrombocytopenia associated with acute and chronic leukemia and with aplastic anemia. In one patient with chronic leukemia and severe thrombocytopenia a rib resection for drainage of a subphrenic abscess was performed with the use of ACTH with the impression that the operative bleeding was less than had been expected.

The role of transfusions, particularly of platelet-rich polycythemia blood with siliconized apparatus or of platelet suspensions in idiopathic thrombocytopenic purpura, is still not clearly defined. Certainly there can be no doubt that blood transfusions must be employed to replace blood lost when there is either peripheral collapse or severe anemia. There is also evidence that in some patients remission may be obtained, usually transiently. Two patients have been reported in whom sustained remission followed blood transfusion[39] but because spontaneous remission occurs in this disorder the possibility of coincidence cannot be eliminated. The chief difficulty with platelet-rich blood and platelet transfusions derives from the studies already mentioned which indicate the development of platelet agglutinins following transfusions, and decreased survival time of transfused platelets following repeated injections. This certainly may limit the value of transfusions and raises the possibility that the patient may be worse off following a series of transfusions than before. At the present time, however, this possibility is purely hypothetic. From a practical standpoint it should be pointed out that few hospitals are equipped to carry out transfusions of platelet-rich blood or suspensions of platelets using siliconized apparatus.

The most important decision in the handling of patients with idiopathic thrombocytopenia concerns whether and when to subject the

patient to splenectomy. As has already been indicated the appearance of the bone marrow does not have significant prognostic value in this decision. In his early studies Schwartz[19] came to the conclusion that some patients with idiopathic thrombocytopenia had greater eosinophilia of the marrow than others. He believed that these patients had a better prognosis both as to the possibility of spontaneous remission and as to the beneficial effects of splenectomy. More recent studies[8] have come to the conclusion that although eosinophilia of the marrow tends to make the prognosis better the correlation with either spontaneous remission or with beneficial effects of splenectomy leaves much to be desired. As to our own experience, at first we were optimistic concerning the usefulness of the response to hormonal therapy as a guide to prognosis following splenectomy. Recently, however, we have encountered two patients who showed satisfactory remissions with hormonal therapy but who relapsed following splenectomy. This lack of correlation has also been pointed out by other workers.[55]

Thus the decision with regard to splenectomy involves weighing the possibilities of spontaneous remission and of a serious hemorrhagic episode, particularly a cerebral vascular accident, during the period of conservative management against the operative mortality of splenectomy and the probability that it will afford incomplete or no relief in as many as one-third of the patients.[22,23] Inasmuch as in adults spontaneous remissions in idiopathic thrombocytopenic purpura seem to occur in only about one-third of all patients, the weight of evidence favors splenectomy.[22,23] How long to delay splenectomy is also a difficult decision. Hirsch and Dameshek[23] in their series appear to indicate the wisdom of delaying splenectomy for approximately four months in most patients with mild to moderate purpura. During this period of expectant management hormonal therapy and transfusions may be helpful.

Following splenectomy without hormonal preoperative preparation the capillary fragility improves within hours[48] but the platelet count usually does not rise to significant heights for several days. In most patients the highest platelet counts are encountered during the second week following splenectomy. Unfortunately, approximately one-third of all patients will subsequently relapse to the point at which their hemorrhagic manifestations again become of clinical significance. Many of this latter group will, however, show a milder hemorrhagic tendency than was present before splenectomy. If the hemorrhagic manifestations following splenectomy are fulminating, therapy with ACTH or cortisone may be resumed[56] and transfusions used to replace blood lost. When menorrhagia or metrorrhagia appear to threaten life, androgen therapy, x-ray castration and even hysterectomy may be considered. Certainly in the face of a fulminating hemorrhagic tendency the last mentioned must be considered only as a final resort.

In the therapy of the thrombocytopenic purpuras a controversial point has been the use of toluidine blue and protamine sulfate to neutralize a "heparin-like" substance said to exist in the blood of some patients.[57] This controversy involves many patients with thrombocytopenia although originally the heparin-like substance was said to be present most often when the thrombocytopenia was the result of irradiation. Recent studies on the hemorrhagic diathesis following irradiation have pointed to the important role of the thrombocytopenia and have minimized the significance of any anticoagulant.[58] In such studies as we have conducted we have been unable to demonstrate an anticoagulant in patients with thrombocytopenia and have not been impressed with the usefulness of toluidine blue or protamine sulfate.

SUMMARY

1. The differential diagnosis, pathogenesis and treatment of the thrombocytopenic purpuras have been reviewed, particularly with regard to recent literature.

2. Bone marrow aspiration is most useful in differentiating those diseases in which there is mechanical displacement of the megakaryocytes from idiopathic thrombocytopenic purpura. It has not been useful in distinguishing idiopathic thrombocytopenic purpura from toxic, infectious, allergic or splenomegalic purpuras. It has not been found to be of significant value in predicting the results of splenectomy.

3. Considerable progress has been made in our understanding of the pathogenesis and of the hemostatic defect in idiopathic thrombocytopenic purpura. The most recent evidence favors the existence of a platelet agglutinin in many patients with this disorder. In several patients this agglutinin has been found to per-

sist following splenectomy. This may explain the occurrence of congenital thrombocytopenic purpura in the offspring of splenectomized thrombocytopenic mothers.

4. The possibility of platelet iso-agglutination phenomena, similar to those due to iso-immunization for red cells, is discussed.

5. The improvement in capillary fragility and thrombocytopenia by use of ACTH and cortisone is reviewed.

6. The treatment of secondary thrombocytopenic purpura in which megakaryocytes are mechanically displaced must be directed against the primary bone marrow disorder. If this disorder is malignant in nature, some transient beneficial effects may be obtained with the use of transfusions, preferably of platelet-rich blood, and with the use of ACTH and cortisone.

7. The treatment of infectious, toxic or allergic purpuras should be directed toward such therapy as may be available for the infection and toward the removal of the offending chemical or physical toxin and search for and removal of the suspected allergen. Again the use of transfusions and hormonal therapy may be considered. Splenectomy should be considered only if conservative management fails.

8. In splenomegalic thrombocytopenic purpura the primary disease responsible for the splenomegaly will usually be unaffected by splenectomy. However, splenectomy may be considered in this group when thrombocytopenic purpura appears to threaten the life of the patient.

9. The management of idiopathic thrombocytopenic purpura in children should probably be expectant as most children will have a spontaneous remission.

10. In adults the treatment of idiopathic thrombocytopenic purpura should be expectant for at least four months except when such management appears to menace the life of the patient.

The results of expectant management may be somewhat improved by the use of transfusions (preferably of platelet-rich blood or of platelets with siliconized apparatus) and by the use of ACTH or cortisone. These hormones, however, probably have their greatest place in the management of hemorrhagic emergencies and in the preoperative preparation of patients for splenectomy. Although normal or increased megakaryocytes are desirable features in the marrow before splenectomy is to be considered, their presence does not guarantee a successful result nor does the occurrence of decreased megakaryocytes forebode an ominous result. The occurrence of eosinophilia of the marrow also improves the prognosis both with regard to spontaneous remission and the effects of splenectomy. However, the correlation between eosinophilia and prognosis leaves much to be desired. Splenectomy results in "cure" of approximately two-thirds of adults with idiopathic thrombocytopenic purpura. When splenectomy fails completely, ACTH, cortisone, androgen, x-ray castration, emergency hysterectomy and transfusions are therapeutic measures to be considered.

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Conference on Therapy

Treatment of the Patient in Coma

THESE are stenographic reports of conferences by the members of the Department of Pharmacology and of Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, Cornell Conferences on Therapy, by the Macmillan Company.

DR. HARRY GOLD: I should like to make a few remarks of an historical nature on these Conferences. These Conferences at the New York Hospital-Cornell Medical Center were started sixteen years ago. There has been a series every year and a few extra ones were inserted in the period of the accelerated schedule during World War II.

Of the two disciplines, that having to do with the diagnosis of disease and that having to do with treatment, the latter is by far the older. Diagnosis was a pretty arid field at a time when the field of treatment was rich with vegetation, mostly weeds to be sure. The rapid growth of interest in and development of diagnostic skills and methods during the middle of the last century soon cast a shadow over the field of therapeutics and in this shadow the art of treatment gradually withered and decayed. Its decline was signalized in the medical schools by the recession of interest in the teaching of therapeutics. Many years have passed since the termination of the last professorship of therapeutics here at Cornell. The suggestion for its revival a few years ago was not favorably received. The symbol of a medical discipline which seemed to be dead was not especially attractive, not so much because it was dead but because its decline was associated with decay. Things began to happen in this area in the early decades of the present century. Science became extremely busy in the field of therapeutics. Important activities not only in animal pharmacology but also in clinical pharmacology led to developments in therapeutics which commanded attention. These Conferences were the answer to an urgent need for discussion and review of a field that was growing very rapidly. It was in 1936 that Dr. DuBois of the Department of Medicine, Dr. Cattell of the Department of Pharmacology and some of the rest of us who were involved in these problems laid the plans to provide a medium for talking over older issues of therapeutics as well as the newer developments. This marked the beginning of the Cornell Conferences on Therapy. Therapy had again become a living subject and it was believed that the Conferences on Therapy would provide a highly elastic medium of exchange of experience and opinion not likely to be provided by either books or formal lectures. For those who are here for the first time, I might add that the Conferences are recorded by a stenotypist, they are edited, and are published in the New York State Medical Journal and the American Journal of Medicine. Some of the Conferences which appear to have more lasting qualities are put together in the form of an annual volume and published by the Macmillan Company. Five of these volumes have already been published. You might be interested in knowing that more than 25,000 of these volumes are in the hands of readers.

I will turn the session over now to Dr. George Reader who will tell you about this Conference.

DR. GEORGE READER: The subject of this Conference is the treatment of the patient in coma. Dr. Harold Wolff has arranged a symposium.

DR. HAROLD G. WOLFF: Dr. McDowell, will you start off and tell us some of the general things you do with patients in coma, also more especially with those in whom the cause is mechanical trauma. I hope you will not mind my asking you a question from time to time.

DR. FLETCHER MCDOWELL: Of first importance among the measures which apply to all patients in coma is maintenance of a clear airway. This is usually accomplished by removing secretions from the mouth and pharynx by suctioning and by inserting an oral airway. Intubation or tracheotomy may occasionally be necessary. If shock is present, it should be treated with whole blood, plasma, or both. Drugs which

produce vasoconstriction, such as neosynephrine, may be of value. The electrolyte balance must be maintained, with particular attention to the possibility of renal failure which is sometimes associated with lowering of the blood pressure or dehydration following head injury, vascular accidents, poisoning and cerebral ischemia associated with increased intracranial pressure. If coma persists for a long time, attention must be paid to nutrition and to an adequate intake of protein. Comatose patients are turned frequently to prevent hypostatic congestion and also to prevent the breakdown of the skin in areas of pressure. Catheterization is usually required, and continuous drainage with an indwelling catheter is desirable until the patient is able to void by himself. Prophylactic penicillin therapy is used to lessen the chances of pneumonia associated with hypostasis and aspiration.

In the case of patients who are unconscious as a result of mechanical trauma, epidural and subdural hematoma should always be suspected. It is necessary to determine as soon as possible whether surgical treatment is needed. Neurologic examinations may give some idea as to the presence and localization of these lesions but observation of the pulse, blood pressure and respiratory rate for a few hours may be necessary to determine whether the patient is becoming worse or is stabilizing. Worsening of the clinical state with elevation of blood pressure and a drop in the respiratory and pulse rate is good indication for surgical investigation of patients who have had head injury. When epidural or subdural bleeding is diagnosed or suspected, bilateral burr holes through the skull, with evacuation of blood from the epidural or subdural spaces, should be carried out as soon as possible. Supportive therapy is given to the patient who is unconscious following head injury but shows no evidence of these lesions. These patients should be observed closely and examined frequently for evidence of collections of blood in the epidural and subdural spaces until consciousness returns, as these may not be evident on original examination. The unconscious state following head injury may persist for as long as six to seven weeks before recovery occurs.

DR. WOLFF: Is increased intracranial pressure the cause of the coma in all patients with head injury?

DR. MCDOWELL: No, coma following mechanical trauma may be associated with cortical laceration, small hemorrhages in the brain substance and often occurs without gross structural change.

DR. WOLFF: Dr. Dunbar, do you treat all patients with post-traumatic coma for increased intracranial pressure, or do you reserve treatment only for those who present specific signs of increased pressure?

DR. HOWARD S. DUNBAR: Usually one does not have to be concerned with the problem of intracranial pressure until anywhere from six to twenty-four hours after an acute head injury, for it is in that period that increased intracranial pressure may manifest itself in association with subdural or epidural hematoma.

DR. WOLFF: In those patients in whom it is desirable to diminish intracranial pressure, do you favor the use of concentrated magnesium sulfate by rectum?

DR. DUNBAR: I think that most surgeons have abandoned the practice since increased intracranial pressure as such is not often the central problem.

DR. WOLFF: However, I take it that if intracranial pressure is increased, you do take measures against it, and as I understand you treat it by drainage.

DR. DUNBAR: Yes, we usually use one or another form of drainage by lumbar puncture.

DR. WOLFF: Have you anything to add to this, Dr. McDowell?

DR. MCDOWELL: I agree that dehydrating substances such as hypertonic glucose solution by vein or hypertonic magnesium sulfate by rectal drip are not especially useful. However, if there is extremely high intracranial pressure associated with subarachnoid bleeding, there may be some advantage in lowering the intracranial pressure by means of spinal drainage, over a period of from thirty to sixty minutes, to about one-half of the pressure recorded at the beginning of the procedure. This measure occasionally restores consciousness and vital signs may return to more normal values following it.

DR. WOLFF: What about attempting to reduce intracranial pressure in patients in coma due to neoplastic masses?

DR. MCDOWELL: Patients in coma due to intracranial expanding lesions should be treated surgically by removal of the mass after localization or by decompression. There are occasions when it may be necessary to postpone surgery

for a few hours, and the reduction of the intracranial pressure by 50 cc. of 50 per cent glucose solution slowly (5 cc. per minute) by vein may make delay safer by restoring vital signs to more normal levels and by possibly eliminating coma. Half-saturated solutions of magnesium sulfate given by rectal drip will often produce the same effect but this method is rarely used because of the possibility of magnesium intoxication.

DR. WOLFF: On those rare occasions when you do use it, how much do you give?

DR. DUNBAR: We use a 25 per cent solution of magnesium sulfate by rectum with the Murphy drip, 300 cc., and give it at a rate of not more than 60 drops a minute.

DR. WOLFF: Do you ever use a more concentrated solution of magnesium sulfate?

DR. DUNBAR: No, it is dangerous. We had one death from a stronger solution, apparently due to magnesium sulfate poisoning. The blood magnesium rose to high levels.

DR. GOLD: Perhaps it would be better to say: Beware of giving too much magnesium sulfate. I have a notion that it was the excessive amount rather than the concentration.

DR. MCDOWELL: Do you ever use hypertonic glucose by vein for reducing intracranial pressure?

DR. DUNBAR: No, we do not.

DR. WOLFF: How about high temperature as a cause of coma?

DR. MCDOWELL: Elevation of the body temperature to very high levels in such states as heat stroke and heat exhaustion is usually associated with stupor or coma. Temperatures may be rarely as high as 114°F. but usually are found to be from 104° to 108°F. Treatment is directed toward lowering the body temperature rapidly to levels compatible with life. This can be done by placing the patient in an ice water bath, by cold water (40°F.) enemas, by packing the patient in ice bags, or by frequent sponging with 70 per cent alcohol until the temperature declines to around 102°F. Care must be taken to avoid the hypothermia which sometimes follows this treatment as it may be as threatening to life as the elevated temperature. As the temperature declines consciousness usually returns.

Coma or stupor may occur with heat exhaustion but in this state changes in mentation are usually associated with vascular collapse and dehydration rather than extreme elevation of body temperature. This condition is treated by intravenous fluids and transfusion of whole blood or plasma. Intravenous fluid and blood should be administered with care, as pulmonary edema often follows their use in this state.

Marked lowering of the body temperature is usually accompanied by stupor or coma. Patients have been reported with rectal temperatures as low as 62°F. with survival but the usual range of temperature with hypothermia is 90 to 95°F. Treatment is directed towards combating shock with whole blood or plasma, treatment of cardiac arrhythmias, and elevating the body temperature to normal levels. The latter seems to be most safely accomplished on patients with profound lowering of rectal temperature by placing them in a cool atmosphere and allowing a slow return, over a period of eight to sixteen hours, of the temperature to normal. With less marked lowering of the body temperature rapid warming and elevation of body temperature to normal over one to two hours has been successful.

DR. WOLFF: Are fluids essential in these cases?

DR. WILLIAM W. SCHOTTSTAEDT: The replacement of fluid loss is clearly necessary if the patient has retained the sweating mechanism and therefore loses fluids through the sweat.

DR. WOLFF: Suppose you saw a patient in coma and with a high temperature, how much fluid would you give?

DR. SCHOTTSTAEDT: One might start with 1 L. of 5 per cent glucose in physiologic salt solution by slow intravenous drip, and give as much as may be necessary.

DR. WOLFF: Dr. McDowell, would you tell us something about the patient in coma from electric shock?

DR. MCDOWELL: The state of patients who are unconscious following electric shock is usually complicated by respiratory arrest or cardiac arrhythmia, such as ventricular flutter or fibrillation. With respiratory arrest which is often associated with shock, by high frequency alternating current, artificial respiration either manually or mechanically is given after an open airway is provided. This is continued until spontaneous ventilation returns. Little can be accomplished in patients with ventricular fibrillation or cardiac arrest. With unconscious patients who have no respiratory or cardiac abnormality following electric shock, supportive measures applicable to any unconscious patient are given until consciousness returns.

DR. WOLFF: There is a growing interest in being certain that the patient in coma is

properly ventilated, i.e., getting enough oxygen and ridding himself of carbon dioxide. Does this interest in proper ventilation have the support of results in practice? Should we converge our efforts especially on this aspect of care?

DR. DUNBAR: I do not think the matter of adequate airways and proper ventilation can be overemphasized. It applies to patients who have had a severe head injury as well as to those who have had operation for brain tumor, which really means brain trauma. We have found that any considerable period of hypoxia proves disastrous. More and more has this commanded the attention of neurosurgeons and others dealing with these problems. In point of fact when there is any question of the airway being clear, even after intubation or any other measure, one does not hesitate in these cases to perform a tracheotomy immediately as an emergency measure. One should never leave a patient with head trauma in the unconscious state without making absolutely certain that the airway is free at all times.

DR. WOLFF: Does this mean tracheotomy in most instances?

DR. DUNBAR: No, it means unremitting attention by the nursing personnel.

DR. WOLFF: We now come to the question of coma caused by drugs usually taken by persons who intend suicide. Dr. Cardon, will you discuss this point? First, what drugs are most commonly encountered in this connection?

DR. PHILIPPE V. CARDON, JR.: The ones that are most apt to cause coma and are amenable to treatment are the hypnotics. Of course any drug that can cause death causes coma. The barbiturates are most commonly encountered. They are sometimes taken accidentally as an expression of automatism but usually the problem is one of attempted suicide. Most of these patients do not take a fatal dose. They usually present the appearance of sleeping peacefully. The breathing is apt to be regular and adequate, although sometimes stertorous. The color is usually good. There may be the smell of alcohol which some of these patients take in addition, although in the usual case there is no smell of alcohol. These patients are usually found in bed; they are likely to be brought in lightly clad or in their night clothes. I mention this point for if they are found in the bathroom or in the street, one needs to entertain the suspicion that the coma may be due to causes other than barbiturates. If the intention is to have a long sleep or even to die in sleep, the patient is likely to lie down for the purpose. The first thing to do is to estimate the depth of the anesthesia. Determine the response to noxious stimuli, digging the knuckles into the sternum or pressing the thumb hard up against the supraorbital region. If the narcosis is not deep, if the result is a grimace or a movement, one does not need to worry about the recovery of such a patient provided he is kept from absorbing any more of the drug. Next wash out the stomach. We use a large tube. The Levin tube is not sufficient, the flow through it is too slow. Use a stomach pump or a large Crump tube; if neither is available, an enema tube. If it is inserted into the side of the nose with most room, a nosebleed is likely to be avoided. It is well to have the patient lying on his left side with his head hanging over the edge of the bed with the face down so that, should reflex vomiting occur with the passage of the tube, the material will go on the floor and not into the lungs. The tube is passed to a depth of 2 feet. Of course make sure it is in the stomach. The washing should be done with the most readily available material; tap water is as good as any. It is poured down through a funnel, a pint at a time. The patient is swung back again, sloshing the water around in the stomach. Then the fluid is removed by gravity siphoning or with the stomach pump. The procedure is repeated with at least 6 pints of water, or is continued until the return is clear.

DR. WOLFF: Do you think you get much of the drug out by this lavage procedure?

DR. CARDON: A fair amount.

DR. GOLD: Do you think that would still be the case when the patient swallowed the drug four or five hours previously?

DR. CARDON: It is amazing to see how much barbiturate can be found in the stomach even after thirty-six hours.

DR. GOLD: Would you say as much as 5 per cent of the dose is found as late as that? You see, if 100 mg. remains in the stomach, the fluid will be strongly positive for barbiturate, but of what significance is that for a patient who has swallowed 2,000 mg. or more? I am inclined to question the value of lavage many hours after the drug was swallowed. I believe that when a patient is seen in fairly good condition five or six hours after the dose is taken, it is quite unusual, if it ever occurs, that the narcosis will deepen in the hours that follow. If the reflexes

are present at the time the patient is seen they are likely to remain so for some hours and then become more active rather than more sluggish.

DR. CARDON: I agree that there may not be a great deal of the drug present at that time but do you believe there is any appreciable risk in the lavage which is carried out with the patient in the proper position?

DR. GOLD: I do not know how great the risk is but aspiration pneumonia is a very real complication. It may well be one of the causes of the fever in barbiturate poisoning. When the tube is in the stomach and the lavage is being carried out, it is not at all rare for fluid to well up into the throat around the tube, and when the patient is in deep narcosis, one cannot depend on the vocal cords to prevent at least some of it from going down into the lungs. Perhaps some does go down into the lungs more often than we suspect, although the amounts may be too small to cause serious trouble.

DR. CARDON: I incline to the belief that with proper positioning of the patient the risk is nil.

DR. WOLFF: This regimen has been used in about 200 patients, I understand, has it not?

DR. CARDON: That is correct.

DR. WOLFF: There seems to be some difference of opinion about its usefulness but let us grant that the procedure might be useful and if done skillfully does not place the patient in jeopardy. What comes after that?

DR. CARDON: When the degree of narcosis is fairly light you can be quite confident that the patient will sleep it off. Patients in barbiturate coma of a depth which leaves intact the response to noxious stimuli get well without further specific therapy if the stomach is washed, an adequate airway established and prophylactic chemotherapy against infection is given.

DR. WOLFF: Tell us more about the airways. This seems to be a very important topic in this discussion of coma.

DR. CARDON: I think it is of major importance and the details of the mechanics are equally important. One or another, or all of the following points help to determine that the airway is inadequate: the presence of cyanosis, respiratory retraction at the neck or intercostal muscles, dissociation of diaphragmatic from intercostal movements, audible wheezes or ronchi, stertor, large quantities of secretion in the oral pharynx. The simplest maneuver and the one that should always be tried is that of extending the patient's head backward and pulling the angle of the jaw forward with the finger and the thumb. This frequently makes the difference between the patient who is barely breathing and one who perks up, whose low blood pressure returns to normal and who very promptly begins to look like one who is going to recover. If the respiratory obstruction is too much to be relieved by the neck maneuver, we use the suction apparatus. The catheter is passed through the nose as quickly as possible plunging it deeply into the oral pharynx. In comatose patients it will often go directly into the trachea. It is well to pass it down as far as it will go. If the cough reflex at the level of the larynx is absent, intubation should be performed immediately. The presence or absence of the cough reflex at the larynx is detected during passage of the catheter for the purpose of suction. Proper intubation should have the services of an expert anesthesiologist. Under direct laryngoscopy he inserts the intratracheal tube and secures it. Through this a suction tube can then be passed to deliver material from regions deep in the lungs. When the cough reflex returns or the patient begins "to ride" against the tube, the intratracheal tube should be removed, again we believe by the anesthesiologist who should stand by for about a half hour for any signs of laryngeal edema which sometimes supervenes. Faint coughing motions in response to the irritation by the aspirating catheter from the region of the carina have no practical significance, for these may persist even in the preterminal stages of the narcosis. The tube should be scrupulously cleaned at frequent intervals and should be removed and cleaned by the anesthesiologist every twelve hours.

DR. WOLFF: I take it that the color of the patient alone is not a sufficient index of an inadequate airway and that the behavior of the accessory muscles may indicate significant obstruction even when gross cyanosis is absent.

DR. CARDON: That is right.

DR. GOLD: To what proportion of patients in barbiturate poisoning does the procedure of intubation apply, would you say 1 to 200?

DR. CARDON: I would guess that figure to be about correct.

DR. WOLFF: The rest of them, I take it, manage to recover without it.

DR. CARDON: One point more, I think what kills people in barbiturate poisoning is anoxia rather than primary paralysis of the respiratory center by the drug. Once the anoxia is con-

trolled it is the very rare patient whose condition will fail to show a striking improvement.

DR. WOLFF: This procedure should be of considerable importance to the ambulance surgeon who sees the person alive. I refer to those situations in which the patient dies by the time he arrives at the hospital or accident room. How about the use of analeptic drugs in these cases?

DR. CARDON: I should like to invite discussion on this point from some of the others here. At the Bellevue Hospital psychiatric service they have gotten on without these drugs in the last four years.

DR. WOLFF: To what drugs do you refer?

DR. CARDON: Picrotoxin, the drug of this group which is usually chosen by those who use analeptics.

DR. WOLFF: Does this mean that they did not find them useful, or that they have found them dangerous, or both?

DR. CARDON: They have found them unnecessary. As far as I know there have been very few deaths from barbiturate poisoning on that service in recent years, and they treat many cases.

DR. DUNBAR: Do you happen to know the death rate from barbiturate poisoning in the United States?

DR. GOLD: I do not know that figure. We probably could get figures on the total number of deaths from barbiturate poisoning but the picture would not be a complete one because we could probably not get a good figure for the number of survivors from barbiturate poisoning.

DR. MCKEEN CATTELL: I wonder what you would do in the case in which poisoning is so far advanced that even with adequate airways established by intubation and suction, fatal poisoning threatened, for there must be cases of barbiturate poisoning in which more than a fatal dose has been absorbed.

DR. CARDON: I would then give picrotoxin intravenously in doses of 3 mg. and repeat it at intervals of a minute, watching carefully for signs of twitching of facial muscles in order to discontinue the dosage before convulsions occur.

DR. GOLD: It has been satisfactorily demonstrated that animals can survive two to three times the ordinary fatal dose of the barbiturates when properly treated with picrotoxin. The use of picrotoxin therefore rests on a sound pharmacologic base. Proof of its value in humans is hard to obtain because the amount of barbiturate taken in most attempts at suicide is apparently not enough by itself to cause death and if these patients are treated in the detailed manner described, the vast majority of them will recover without picrotoxin. I should think it would be a mistake, however, to treat a patient in advanced barbiturate poisoning in whom all reflexes have vanished without a satisfactory regimen of picrotoxin. I believe it is in this very group that we are likely to obtain the evidence we need which may show that when more than a fatal dose of barbiturate has been absorbed by a human he may respond to picrotoxin like the animal, and survive. I think the dosage of 3 mg. recommended is too small.

DR. WOLFF: How much would you give?

DR. GOLD: I should use 10 mg. of picrotoxin intravenously every ten to fifteen minutes until the excitant effect of picrotoxin becomes manifest.

DR. WALTER F. RIKER, JR.: What is the chance that the patient will go back into coma after the effect of the analeptic wears off?

DR. CARDON: Recurrence takes place, but as the stimulant effect begins to wear off, additional doses are given to continue the analeptic action until enough of the depressant is eliminated.

DR. WOLFF: It is apparently the consensus that picrotoxin may be useful but is not commonly needed.

Let us turn now to another topic. Dr. Hinkle, will you discuss diabetic coma very briefly.

DR. LAWRENCE E. HINKLE, JR.: The patient with diabetes mellitus may become unconscious because of acidosis or because of insulin hypoglycemia. There are those in whom the gradual development of acidosis has simply escaped detection, those who omit the necessary doses of insulin and those in whom exacerbation of the diabetic syndrome has taken place as the result of particular stresses. In the elderly stable individual the stress is usually in the nature of a trauma or some intercurrent illness. In these it is important to recognize that diabetic acidosis is more apt to be due to a complicating condition than to spontaneous advance of the diabetes, and to make a careful search for such complicating conditions. In the younger and more labile individual a stressful life situation is usually responsible. Diabetic coma develops slowly. It is accompanied by a period of negative fluid balance with thirst and polyuria. There is usually

nausea, vomiting and drowsiness increasing over periods of hours or days prior to the loss of consciousness. In the advanced stage there are signs of pronounced dehydration and Kussmaul breathing. In the terminal situations there is vascular collapse. The diagnostic information which is most readily available and most useful is obtained from a test of the urine which usually shows both sugar and acetone. In instances of extreme oliguria the acetone may be absent but this is rare.

In making the diagnosis it is of course necessary to exclude the other causes of coma, some of which have been mentioned in this conference. Hypoglycemia causing coma in the diabetic patient is an important source of error. Salicylate poisoning is of some interest because it is associated with acidosis, hyperpnea, and with a false positive ferric chloride reaction in the urine. On the other hand, however, the urine is free of glucose, the nitroprusside test is negative and the condition is not associated with dehydration.

The treatment of diabetic acidosis is chiefly a matter of giving sufficient insulin, glucose and salt water. In this hospital we always use regular or crystalline insulin of the fast-acting variety. We examine the urine every half hour, and in the patient in coma we obtain these samples through an indwelling catheter. We administer 25 units of insulin every half hour, the initial dose intravenously if the patient is in vascular collapse or if there is any reason to suspect that it may not be absorbed from the subcutaneous injection. We set up an intravenous infusion of 5 per cent glucose in physiologic salt solution, and give 1 or 2 L. in the first hour, thereafter about 500 cc. per hour. It is of course important to avoid overloading the cardiovascular apparatus. Glucose is used together with insulin because the combination is markedly antiketogenic. We avoid the use of stronger than 5 per cent solutions of glucose because they disrupt the osmotic equilibrium of the blood. This treatment is continued until the ketone bodies disappear from the urine. We actually continue the doses of insulin for an hour and a half after the ketone bodies disappear.

DR. WOLFF: Is not the treatment directed toward the return of consciousness?

DR. HINKLE: That is so, but the guide to treatment is the disappearance of ketone bodies from the urine, the return of consciousness taking care of itself.

DR. WALTER MODELL: How about the sugar in the urine?

DR. HINKLE: The presence of sugar in the urine in the course of treatment is a matter of indifference. It is the presence of ketone bodies which indicates trouble and it is the disappearance of the ketone bodies which points to the fact that the results are progressing as they should.

When consciousness returns we remove the catheter and administer fluids by mouth using such materials as a glass of orange juice and salt broth alternately. Occasionally thirty-six hours after treatment with glucose-insulin is started the patient may develop hypopotassemia with return of collapse. This may be prevented in the conscious individual by the oral fluids, orange juice and salt broth, and if need be, 1 or 2 gm. of potassium chloride may also be administered by mouth.

DR. WOLFF: Dr. Hinkle, since the two opposite causes of unconsciousness, hypoglycemia and hyperglycemia, are sometimes confused, is there a quick and ready means for distinguishing them in the patient that one might encounter on the street?

DR. HINKLE: The presence or absence of physical signs of dehydration is helpful. In the hyperglycemic person the coma is associated with dryness of the skin and soft sunken eyeballs. The person with hypoglycemia is apt to be cold and sweaty; he may also be in convulsion.

DR. WOLFF: Would you tell us how to treat the hypoglycemic state and how to bring such a patient "back" with the greatest of speed?

DR. HINKLE: A dose of glucose intravenously returns such a patient to consciousness rapidly. If the hypoglycemia is associated with protamine insulin, it will be necessary to take glucose by mouth for several hours to insure against relapse to unconsciousness.

DR. MODELL: Have the fancier solutions like one-sixth molar sodium lactate been given up completely?

DR. HINKLE: Some use it.

DR. WOLFF: Do you use it?

DR. HINKLE: It is available here in the hospital *a la carte*. We do not think it is necessary.

DR. WOLFF: Dr. Schottstaedt, will you help us out with that special collection of conditions in which coma is related to a disturbance in electrolytes with or without renal disease?

DR. SCHOTTSTAEDT: Coma may result from depletion of water and salt, each alone or in

combination. The case with simple water deficit is commonly seen in elderly debilitated patients who may take too little water either because they are too weak or unable to make their wishes known. They may have water at their bedside but may be able to take only a few sips at a time. When this deficit becomes extreme, the patient may go into coma. This is treated by intravenous infusion of 5 per cent glucose in water rather than by physiologic salt solution, because the fluid loss in these cases is largely by way of insensible perspiration which is almost entirely water, the urine volume being very low.

In cases in which there is a source of considerable salt and water loss, such as vomiting, diarrhea and profuse sweating, physiologic salt solution is the better material for replacement. In such cases the losses of salt and water are usually very marked before coma supervenes. As the condition develops the patient shows a number of symptoms, weakness, lassitude, muscular cramps, giddiness, orthostatic fainting, stupor and coma. A liter of physiologic salt solution is given intravenously fairly rapidly in about an hour, and 3 to 4 L. may be given in the first twenty-four hours if necessary. Again, one has to watch out for signs of overloading of the circulation and one should turn to oral fluid as soon as possible.

The amount of salt loss with a particular amount of water depends upon the channel through which the fluid loss takes place. If the fluid loss is largely through sweat, which is quite hypotonic, the replacement is made partly by means of physiologic salt solution and partly by means of glucose in water.

Conditions associated with dehydration and circulatory failure, concussion injuries or intravascular hemolysis may result from renal shutdown with marked oliguria or anuria. When the blood pressure falls to about 60 mm. of mercury, it is believed that intense renal vasoconstriction occurs, in consequence of which glomerular filtration may cease and if this continues long enough tubular damage ensues. In some of these cases diminished or absent urine flow may persist even after the original cause is removed. The possibility of renal shutdown must be considered in all cases of coma. The first measure is to treat the shock. Fluids help to restore the renal function but in these cases it is especially important to avoid overhydrating. If there is renal shutdown due to a temporary circulatory collapse but the patient is conscious, it is well if possible to follow the course of treatment by the patient's daily weight. It is well to give only so much fluid as will restore the weight present before the episode which produced the anuria. One might bear in mind the fairly constant source of fluid loss in these cases, namely, the loss by insensible perspiration. It amounts to about 1 L. a day. It is almost entirely water and should be replaced by 1 L. of 5 per cent glucose in water. The 50 gm. of glucose a day given in that manner supplies a few calories and cuts down the protein loss. Then there is the fact that the glucose breaks down into water and carbon dioxide which is excreted by way of the lungs. If instead this patient receives physiologic salt solution, he is in a sense "stuck" with the salt which requires renal action for excretion.

DR. WOLFF: Patients sometimes develop coma in connection with heart failure. Dr. Gold, you have been working in this category, would you like to say a word about it? Is there any agent that one can depend upon to restore the circulation promptly?

DR. GOLD: In general the patient in whom an attack of syncope develops in connection with a cardiac problem had better be left to come out of it spontaneously. The less fuss with drugs the better. I have reference to such situations as syncope with an acute attack of coronary thrombosis, some paroxysms of rapid ectopic rhythm, attacks of heart block with Adams-Stokes syndrome, and vasovagal syncope. Occasionally one can restore consciousness by restoring the heart beat in periods of asystole or ventricular fibrillation by an intracardiac injection of 0.5 cc. of 1:1000 solution of epinephrine with cardiac massage. In cases of recurring attacks of syncope which may come on every few minutes in patients with heart block there is the problem of preventing attacks and for this purpose ephedrine sulfate is probably the most useful agent. A useful regimen is to begin with a dose of 30 mg. three times daily and increase the dose as necessary until the daily dosage is adequate to bring the attacks under control. This is a fairly large subject and we should need a great deal more time to handle it more satisfactorily.

DR. WOLFF: Thank you. Dr. Rennie, there are a certain number of people, I am sure there are a great many more than we diagnose, who are put into states resembling coma as a result of very bad life experiences, shocking experi-

ences, catastrophes, severely traumatic and critical moments. Would you like to tell us how you recognize them and what you do about them?

DR. THOMAS A. C. RENNIE: The psychogenic reactions, of course, are stuporous reactions, therefore, in the sense in which we have used the term, they are not in the category of coma at all since there is no loss of consciousness in these states. On the contrary there is usually a keen awareness of all that is going on around the patient. If one can get a history, there is usually a story of mental illness preceding the stuporous reaction. If not, they are generally clearly enough recognized by the normal vital signs and the usual ample response to pain stimulus. Stuporous reactions are of four major categories, dwindling in incidence, now less frequently seen in psychiatric hospitals. Occasionally they are encountered in accident rooms. They are the schizophrenic or catatonic stupor, characterized by the waxy flexibility, stereotyped mannerism, awkward postures and catalepsy; the depressive stupor which represents the ultimate in depressive slowing although usually combined with a good deal of fear and aversion, something which the textbooks mention but which frankly I have rarely seen; the manic stupor in which a patient becomes so overactive that he finally retreats into a state of inactivity; and finally, the hysterical stupors. All of them, I think, you would easily enough distinguish from the usual comatose states.

Briefly, one gives them adequate physical care in terms of cleanliness, tube feeding, maintaining vital functions, particularly in the schizophrenic stupor which may last for weeks, months or years if not treated by specific measures. One also tries to prevent joint ankyloses by adequate physical medicine and rehabilitation measures. Fortunately, with the use of insulin therapy in schizophrenia, this type of stupor is a very brief-lived affair in most psychiatric hospitals. With electric shock available for the deeply depressed patient, this too is a condition which is usually rapidly corrected. With modern practice in psychiatric hospitals, stupor has practically vanished for the reason that these stuporous reactions represent the ultimate of submissive passive response, and most modern psychiatric hospitals have long ago abandoned authoritarianism in favor of gentle, persuasive, encouraging technics. When they do occur, it is often a reflection on the hospital and its atmosphere.

DR. WOLFF: Is syncope something that you hear about these days?

DR. RENNIE: In psychiatry much less than in medicine and other branches.

DR. WOLFF: Dr. McDowell, one more question. Occasionally persons after epileptic seizures remain unconscious sufficiently long to alarm the family. Have you any recommendations?

DR. MCDOWELL: Coma following an individual seizure requires no treatment other than preventing injury during the seizure. Consciousness usually returns promptly after cessation of the fit. If seizures occur in rapid succession (status epilepticus), unconsciousness is present and continues until seizure activity is stopped. The longer-acting barbiturates such as phenobarbital are the drugs of choice and should be given by vein in doses of 0.1 gm. every twenty to thirty minutes until all seizure activity disappears. If obvious convulsive movements are not present and coma continues, electroencephalographic tracings may reveal that continued seizure activity is present and further anticonvulsant therapy is indicated.

DR. DUNBAR: I would question the desirability of waiting a half hour between the injections of the barbiturate in a patient who is having a series of more or less rapidly recurring fits. We use pentothal.® It can be given either in single, rapidly repeated doses or in the form of an infusion until the fits end. We rarely need more than a total of 0.5 gm.

STUDENT: What does one do for coma in the drunk?

DR. CARDON: First be sure there is alcohol on the breath. Also bear in mind the fact that it may be complicated by a head injury. In my experience even the dead drunk picked up off the street responds to noxious stimuli and shortly after an intravenous dose of 1 gm. of caffeine sodium benzoate it is unusual that he cannot be made to walk.

VISITOR: How about coma due to carbon monoxide poisoning.

DR. CARDON: Get the patient out of the atmosphere of carbon monoxide as quickly as possible and give 100 per cent oxygen inhalation, or oxygen with 7 to 10 per cent carbon dioxide.

VISITOR: How about the patient overly depressed by morphine?

DR. CARDON: Addicts rarely get into trouble because they know the dose that is suitable for them. One occasionally sees a juvenile who gets

into difficulty with the first "shot" of heroin. The treatment is usually supportive and if the respiration is markedly depressed, an adequate airway and artificial respiration in the more advanced cases. Picrotoxin does not seem to be useful here. Caffeine may help to improve the respiration.

DR. GOLD: There is a specific antidote to morphine. It reverses a dangerous depression of respiration in a patient who has been severely poisoned with morphine, meperidine or methadone.

DR. CATTELL: The chemical name is N-allylnormorphine hydrochloride. There is a trade preparation known as nalline® put up by Merck in the form of the solution of the hydrochloride. It is given in intravenous doses of from 5 to 40 mg. depending upon the severity of the poisoning. It is relatively new and one should become familiar with this material because it is possible to produce poisoning with it.

SUMMARY

DR. GOLD: The subject of this Conference, the treatment of the patient in coma, is one that frequently forces itself upon the attention of the practicing doctor. As is usually the case in these Conferences there has been no attempt to exhaust the subject, only to deal with some of the more pressing aspects of it. In this case the approach to the situation has been one of presenting in the most pointed way possible the few items necessary for diagnostic orientation, for a ready decision as to what to do, and something of the details of the therapeutic measures themselves. Such restriction of the subject has made it possible to cover a fairly wide range of conditions causing coma and to present in each case material of practical utility for ready use when the particular comatose patient is encountered: injuries to the head with only concussion; injuries to the head with epidural or subdural hematoma; expanding tumor masses in the brain; acidosis in the diabetic; hypoglycemia in the diabetic; disturbance in electrolyte balance due to renal failure, metabolic and nutritional upsets; syncope in the cardiac patient; coma during status epilepticus; attempted suicide with the barbiturates; and accidental depression by an overdose of morphine. There are discussions of an effective technic for washing the stomach, for dealing with the problems of increased intracranial pressure, for the respective indications for intravenous infusions of sugar water as against salt water, the use of magnesium sulfate and hypertonic solutions in increased intracranial pressure, picrotoxin, caffeine, and the new antidote for morphine poisoning, N-allylnormorphine hydrochloride. A thought which appears and reappears with considerable emphasis in the various sections of the Conference is the extreme importance of maintaining an adequate airway to insure sufficient pulmonary ventilation in the patient in coma from whatever cause. Observations made in the management of various types of coma, whether due to head injuries or attempted suicide with the barbiturates, or any other, have grown into the conviction that one of the commonest causes of disaster in the comatose patient is the failure to establish a sufficient airway. There is discussion in the Conference of the best way to do this.

Clinico-pathologic Conference

Chronic Lymphocytic Leukemia and Recurrent Meningitis*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D. of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, G. S. (No. 188441), was a brewery worker, sixty-five years of age, who entered the Barnes Hospital for the first time on August 28, 1950, because of a shaking chill and fever. The family history was non-contributory. The past history and systemic review were negative except that for eighteen years prior to his first visit to the Washington University Clinics in July, 1947, the patient had been troubled by upper abdominal discomfort with marked eructation and dyspepsia. These symptoms, which were particularly common following the ingestion of milk and pastry, led the patient to present himself at the clinic. At that time physical examination revealed a grade two apical systolic murmur without cardiac enlargement, a palpable liver edge two finger-breadths below the right costal margin, bilateral varicose veins and slight ankle edema. The laboratory work included a normal red blood cell count and hemoglobin. The white blood count was 14,200, the differential showing 2 per cent eosinophils, 1 per cent stab forms, 27 per cent segmented forms, 68 per cent lymphocytes and 2 per cent monocytes. No abnormal cells were described. Complete gastrointestinal studies were negative.

The patient was not seen again in the clinic until December, 1949, at which time he returned because of an exacerbation of his gastrointestinal complaints and because he had also noted a number of moderate sized "lumps" on the right side of his neck which were neither inflamed nor tender. The significant physical findings at this time included numerous enlarged lymph nodes, 2 to 3 cm. in diameter, in the right posterior cervical, right supraclavicular, right and left axillary and right inguinal regions. The nodes were all discreet and of rubbery consistency except those in the right supraclavicular region which were matted. The liver edge was again palpable two fingers breadth below the right costal margin. A hard nodular mass, measuring 3 by 6 cm., was felt just to the left of the umbilicus. It was non-tender and did not move with respiration. Examination of the scrotum revealed small bilateral hydroceles and a varicocele on the left.

The laboratory data were as follows: red blood cell count, 4,000,000; hemoglobin, 13.5 gm.; platelets, 776,000; reticulocyte count, 4.0 per cent; white blood cell count, 18,500; differential count: 1 per cent myelocytes, 1 per cent metamyelocytes, 10 per cent polymorphonuclear leukocytes, 79 per cent lymphocytes, 1 per cent lymphoblasts and 8 per cent monocytes. Bone marrow examination: there was a marked predominance of small, closely packed lymphocytes, and depression of myeloid elements, changes considered diagnostic of chronic lymphocytic leukemia.

The patient was treated with x-ray therapy and there was a marked regression in the size of the lymph nodes and abdominal mass. The total white blood count fell to within normal limits, although the differential count continued to show an increased number of small lymphocytes. The patient was much improved, and was followed periodically in the clinic. On the day of his first entry he had a sudden chill and his temperature rose to 39.7°C. He came to the Barnes Hospital Emergency Room and was admitted.

Physical examination was unchanged from that previously noted except that the pharynx was diffusely injected; no exudate was seen. The routine laboratory data were likewise the same as noted previously. Blood cultures were negative and throat and sputum cultures revealed only Neisseria, coliform organisms and

a few alpha-hemolytic streptococci. The patient was treated symptomatically. His temperature fell to normal in a period of several hours, and he was discharged on August 29, 1950, to be followed in the clinic.

In December, 1950, he received another course of x-ray therapy because of recurrent enlargement of numerous lymph nodes and of the spleen. Once again he made an excellent response. The blood counts were unchanged.

The patient did well then until the morning of his second admission, March 17, 1952, at which time he noted the rather sudden onset of generalized weakness and mild headache. Shortly thereafter he had mild abdominal cramping, and passed several diarrheal stools which were free of blood and mucus. Although he was able to work, he became mentally confused during the course of the day, was noted to have fever and was sent to the Barnes Hospital.

Physical examination revealed the temperature to be 41.1°C., pulse 110, respirations 20 and blood pressure 130/70. The patient was acutely ill and grossly disoriented. A macular rash was noted over the trunk and thighs. Numerous peripheral lymph nodes, measuring 0.5 to 1.0 cm. in diameter, were palpable. They were all non-tender and discreet. The liver edge was again felt two finger-breadths below the right costal margin, and the splenic tip was palpated three finger-breadths below the left costal margin. There were no localizing neurologic signs and the remainder of the physical examination was within normal limits.

The laboratory data were as follows: red blood cell count, 4,150,000; hemoglobin, 12.5 gm.; white blood cells, 41,500; differential: 2 per cent eosinophils, 15 per cent band forms, 7 per cent segmented forms, 75 per cent lymphocytes and 1 per cent monocytes. Moderate anisocytosis and poikilocytosis of the red blood cells was observed. Urinalysis: negative except for an occasional white blood cell and epithelial cell per high-power field in the centrifuged sediment. Stool: guaiac negative. Cardiolipin test: negative. Blood chemistry: non-protein nitrogen, 36 mg. per cent; total protein, 6.0 gm. per cent; albumin, 3.5 gm. per cent; globulin, 2.5 gm. per cent; sodium, 141.1 mEq./L; potassium, 3.8 mEq./L; chloride, 107 mEq./L.; chloride, 107 mEq./L.; carbon dioxide combining power, 29.2 mEq./L.; cephalin-cholesterol flocculation test ±; zinc flocculation test, negative; thymol turbidity test, 7.8 units. Typhoid agglutination: negative. Stool culture: no pathogens.

During the first twenty-four hours following admission the patient's rash became generalized and petechial in character. He became more stuporous and his neck became rigid. A lumbar puncture was performed. The initial pressure was 150 mm. of water, the protein 35 mg. per cent and the sugar 76 mg. per cent. Neither cells nor bacteria were noted in the spinal fluid. Culture subsequently was positive for Neisseria intracellularis. Blood culture taken on admission was also positive for meningococci. The patient was treated with intravenous sodium sulfadiazine and massive doses of penicillin. Chloramphenicol therapy, which had been started at the time of admission, was also continued. The patient received intrathecal penicillin in 10,000 unit doses initially and at the time of a second lumbar puncture the following day. The second fluid contained 1,150 cells, 75 per cent of them polymorphonuclears. Culture was negative. The patient made a dramatic response, and was afebrile within five days of admission. Except for the appearance of fine rales at both lung bases posteriorly, his course was uncomplicated, and he was discharged on March 28, 1952.

After he left the hospital the patient continued to feel rather weak and was bothered considerably by constipation. On a follow-up visit to the clinic it was noted that he had developed several masses in the abdomen; these were thought to represent enlarged lymph nodes. In April, 1952, his red blood cell count was 3,430,000 with a hemoglobin of 9.8 gm. The platelet count was 250,000, reticulocytes 4.2 per cent and the white blood cell count 28,700. The differential count showed 1 per cent eosinophils, 10 per cent segmented forms, 88 per cent lymphocytes and 1 per cent monocytes. In addition to the abdominal masses already mentioned the patient also had 3 to 4 plus pitting edema of the lower extremities and enlarged inguinal lymph nodes. He was given another course of roentgen therapy. Following its conclusion the edema disappeared and the patient noted distinct increase in strength and appetite.

His third admission on July 10, 1952, was occasioned by the development of acute thrombophlebitis and cellulitis involving the right leg. After entry to the hospital he was treated with penicillin and streptomycin. The involved extremity was elevated and immobi-

lized. Once again the patient made a satisfactory response and his signs and symptoms disappeared rapidly. He was discharged on July 15, 1952.

The patient did well until September, 1952. Eight days prior to his fourth admission he developed dull aching and questionable pleuritic pain in the right anterior chest, followed by fever and a cough productive of yellow mucoid sputum. He was seen in the Emergency Room six days prior to entry at which time his temperature was 38.3°C., and a chest x-ray showed findings suggestive of pneumonitis in the right lower lobe. He refused admission and was therefore given repository penicillin therapy as an outpatient. He promised to return daily for additional injections but failed to do so. Three days prior to entry he developed progressive malaise, increase in cough, pleuritic pain across the mid-back and recurrence of fever, and on October 1, 1952, he was admitted for the last time.

Physical examination revealed the patient's temperature to be 40.1°C., pulse 100, respirations 20 and blood pressure 100/50. He appeared acutely ill. The skin was warm and dry but no rash was seen. The neck was supple. Bilateral inspiratory retraction of the intercostal spaces was noted, and percussion and auscultation revealed dullness on the right side anteriorly, laterally and posteriorly over the base. There was a small area of whispered pectoriloquy just lateral to the right nipple. Breath sounds were decreased and moist rales were present over the right lower lung field anteriorly and posteriorly. A few rales were heard at the left base posteriorly. The liver was palpable almost to the level of the right iliac crest. The spleen was not palpable, but one observer described several masses which he interpreted as retroperitoneal lymph nodes in the left upper and lower quadrants. The abdomen was diffusely tender, but there was no spasm. The physical examination was otherwise unchanged from that recorded previously.

The laboratory data were as follows: red blood cell count, 3,380,000; hemoglobin, 11.5 gm.; white blood cell count, 20,800; differential count: 1 per cent eosinophils, 2 per cent myelocytes, 2 per cent juveniles, 8 per cent stab forms, 46 per cent segmented forms, 38 per cent lymphocytes and 3 per cent monocytes. Urinalysis: negative. Stool: guaiac negative. Blood chemistry: total protein, 8.4 gm. per cent; albumin, 3.3 gm. per cent; globulin, 5.1 gm. per cent; non-protein nitrogen, 27 mg. per cent; cephalin-cholesterol flocculation test: 2 plus; thymol turbidity test: 7.8 units; chloride, 98 mEq./L.; carbon dioxide combining power, 30 mEq./L. Chest roentgenogram: There was pneumonitis involving the right middle and right lower lobes, left ventricular enlargement and mediastinal widening. A small lobulated pleural effusion was seen at the apex of the right lower lobe.

Immediately upon entry the patient was started on penicillin and streptomycin therapy. Thoracentesis was attempted without success. Because the sputum culture revealed proteus organisms, terramycin was also administered. On October 5, 1952, the patient became disoriented and incontinent of urine. His temperature rose to 40°C. and stiffness of the neck was noted. A lumbar puncture was performed. The fluid was under an initial pressure of 225 mm. of water and contained 15,000 white blood cells, almost all of them polymorphonuclear leukocytes. The protein was 91 mg. per cent, and the chloride 106 mg. per cent. The specimen for sugar determination was inadvertently lost. A smear of the spinal fluid was reported as showing numerous gram-positive intracellular cocci, but subsequently the culture of the spinal fluid as well as that of the blood revealed Alcaligenes fecalis. Intravenous sodium sulfadiazine therapy was begun, and the penicillin dosage was increased to 1,000,000 units every two hours. The patient continued to be restless and unresponsive and his temperature remained in the vicinity of 40°C. Generalized muscular twitching with some spasticity was observed but there were no localizing neurologic signs. The respirations became Cheyne-Stokes in type.

Following recovery of Alcaligenes fecalis from the blood and spinal fluid terramycin was given by the intravenous route; the other antibiotics were continued. One thousand units of penicillin and 10 mg. of streptomycin were injected intrathecally. Despite these measures the patient continued to be stuporous, his temperature rose to a maximum of 41.3°C. and he expired on October 7, 1952.

CLINICAL DISCUSSION

DR. ROBERT J. GLASER: Because this case is a rather complicated one I would like to begin by

reviewing briefly the course of the patient's illness. This man first came to the Washington University Clinics at the age of sixty, complaining of gastrointestinal symptoms of eighteen years' duration. These may or may not have been related to his major illness. At that time the physical findings were not remarkable. The liver was palpable two fingers breadth below the costal margin, the white count was 14,000 with 68 per cent lymphocytes and the red count and hemoglobin were normal. The patient did not return to the clinic for two years, but when seen the second time he had a palpable liver as before, a distinct abdominal mass and significant lymph node enlargement. On this occasion the white count was 18,500 with 79 per cent lymphocytes. Bone marrow examination confirmed the clinical diagnosis of chronic lymphocytic leukemia. He entered the hospital for the first time about a year or so later because of an upper respiratory infection, heralded by a shaking chill and a temperature of 39.0°C. His pharynx was reddened but there was no exudate. The spleen was palpable and the white count was 25,000 with 85 per cent lymphocytes. The illness was very short-lived; the patient recovered in twenty-four hours without any specific therapy. He left the hospital to be followed in the Out-Patient Department. Several months later he received a course of x-ray therapy at the Mallinckrodt Institute because of lymphadenopathy. Once again his response was good and he was apparently well for another year. The second admission in March, 1952, was occasioned by fever, headache, weakness and diarrhea, all of very short duration. In addition to the physical findings which were consistent with chronic lymphocytic leukemia, the patient also had a rash which spread after he entered the hospital. Meningeal signs developed and a lumbar puncture was performed. Although neither cells nor bacteria were seen on smear, meningococci were recovered from both the blood and the spinal fluid. Dr. Atkins, I believe you were taking care of this patient at the time. Despite the fact that he had no signs of meningitis when he entered the hospital, the rash led you to suggest meningococcemia as a diagnostic possibility. Do you have any comment to make at this point?

DR. ELISHA H. ATKINS: I remember this man very well because he presented such a dramatic clinical picture. The diagnosis of meningococcemia was actually first suggested by the admitting intern in the Emergency Room. When the patient came on the ward, we were not particularly impressed by the skin lesions. If anything, they suggested rose spots. Because the lesions rapidly increased in number and became petechial, it was obvious that the patient did indeed have meningococcemia, and, therefore, the lumbar puncture was performed.

DR. GLASER: The patient was treated vigorously and made a most satisfactory recovery. After he left the hospital he was followed in the clinic, and a month later was given a course of radiation therapy. He then remained well for about three months, re-entering the hospital for the third time because of cellulitis and thrombophlebitis. It was at this juncture that he first began to show evidence of anemia and thrombocytopenia. His response to antibiotics was once again satisfactory, and after leaving the hospital he remained reasonably well until his terminal illness. Because we want to discuss that episode separately and in some detail, I would like to ask Dr. Wilson now to review the patient's films up to that point.

DR. HUGH M. WILSON: The gastrointestinal studies which were made in 1947 are no longer available, but they were reported as negative. The first chest film in December, 1949, showed moderate left ventricular enlargement and some interstitial fibrosis, perhaps no more than usual for a patient sixty-two years of age. There was also bilateral apical scarring. It was at this time that the diagnosis of chronic lymphocytic leukemia was made and the patient given his first course of radiation therapy. In August, 1950, he had another chest film which showed no significant change. When he was admitted in March, 1952, the x-ray studies demonstrated splenomegaly and hepatomegaly, but no change in the chest x-ray was observed. A gastrointestinal series showed changes characteristic of extrinsic pressure on the intestinal tract. The stomach and duodenum were somewhat displaced by what we thought were enlarged retroperitoneal nodes. There was no evidence of intrinsic involvement of the intestines *per se*.

DR. GLASER: As recorded in the protocol, this man's gastrointestinal symptoms began some eighteen years before he developed leukemia. Dr. Harrington, is it reasonable to assume that they were unrelated to the blood dyscrasia?

DR. WILLIAM J. HARRINGTON: That is a reasonable assumption, but one cannot be certain about this point. It is conceivable that

the patient may have had leukemia over this long period of time.

DR. GLASER: Will you say something about the course of chronic lymphocytic leukemia, particularly in patients in the older age group?

DR. HARRINGTON: For purposes of evaluating the prognosis of chronic lymphocytic leukemia in relation to age of the patient, the arbitrary dividing line is at age thirty. Years ago Dr. Minot studied eighty patients with chronic lymphocytic leukemia above the age of thirty; their average duration of life was three and one-half years. In contrast, the course of the disease in a much smaller group of patients under the age of thirty was only one year. When the age of each patient was plotted against the duration of the disease a relatively straight line resulted. It is not unusual, in any clinic where a large number of patients with leukemia are followed regularly, to see patients who have had chronic lymphocytic leukemia for ten or fifteen years. Some patients do well for even longer periods. Certainly many go five, six or seven years before they require any therapy at all. Thus in the patient we are discussing today, it may be that retroperitoneal or gastrointestinal involvement had been present for years and may actually have been responsible for the long history of gastrointestinal symptoms. Custer and Mallory and Gall believe that some patients with chronic lymphocytic leukemia begin with a focal disease which is designated variously as lymphocytoma or lymphosarcoma. Although it is less likely on a statistical basis that this patient had leukemia for eighteen years, the possibility cannot be excluded.

DR. GLASER: If the disease had indeed been present for such a long period, do you think the gastrointestinal tract was intrinsically involved or that the symptoms were due to extraluminal pressure?

DR. HARRINGTON: Many patients with retroperitoneal lymphoma complain of gastrointestinal symptoms not unlike this man's. In such cases postmortem examination frequently does not show intestinal lesions.

DR. GLASER: Dr. Mendeloff, do you have any comments to make on this point? Certainly some patients whose gastrointestinal tracts are distorted by extrinsic pressure do have similar symptoms. Do you believe this is a function of altered motility?

DR. ALBERT MENDELOFF: Your question is a difficult one to answer, Dr. Glaser. Although some patients with distortion of the gastrointestinal tract do have symptoms, others with extreme distortion often are asymptomatic. If a patient with distortion due to extrinsic pressure does complain of symptoms, one cannot be certain the distortion *per se* or some inflammatory involvement at a point of contact is responsible. In the esophagus enormous displacement may result from cardiac enlargement and yet give rise to few or no complaints. In the small bowel, however, where fixation is more apt to occur, symptoms are more common.

DR. GLASER: This patient was found to have some degree of hepatomegaly on his first visit to the clinic. Dr. Harrington, do you believe this finding was due to leukemic infiltration? He worked in a brewery, of course, but his liver function tests were all normal.

DR. HARRINGTON: As I remember this man from the clinic, he was not a "beer-drinking" brewery worker. It is conceivable that he did have leukemic infiltration of the liver. The problem of non-symptomatic leukemic infiltration of various organs is an interesting and important one, particularly as it bears on the treatment of coincidental lesions. For example, a number of patients with chronic lymphocytic leukemia develop dermatitis and ulceration following x-ray treatment. In some instances, plastic surgeons are reluctant to repair such ulcerated lesions because of the underlying disease. Yet, as we have indicated, a significant number of these people may be alive and perfectly well five years later. Therefore, the mere diagnosis of leukemia should by no means contraindicate other therapeutic measures.

DR. GLASER: In discussing the relatively good prognosis of elderly patients with chronic lymphocytic leukemia it is of interest that this patient had at least three infections, two of which were extremely severe. It is pertinent to inquire, therefore, whether patients with lymphocytic leukemia are more prone to infection than those with other forms of the disease. Dr. Chernoff, would you say something about this point, and also comment on the incidence of meningitis in chronic leukemia?

DR. AMOZ I. CHERNOFF: There are few data bearing on the incidence of infection in patients with leukemia, although it is generally accepted that leukemic patients are more susceptible to infection than normal individuals in the same age group. Whether this tendency is due to some basic abnormality in the white cells or not is

unknown, but such an hypothesis is provocative. It is probably true that patients with lymphocytic leukemia are even more prone to infection than those with myelocytic forms. This observation has been explained by some as being due to the presence of larger amounts of myeloid tissue in the latter group, so that when the stress of infection occurs, a more effective leukocytic response is possible. Against this explanation is the fact that patients with lymphocytic leukemia may respond to infection with a significant increase in polymorphonuclear leukocytes in the peripheral blood. In this patient, for example, although his differential counts in general showed a great preponderance of lymphocytes on one occasion, the percentage of granulocytes in the peripheral blood rose to a significant level, suggesting that some functioning myeloid tissue was present and was able to respond to a sufficient stimulus.

DR. GLASER: The particular rise in granulocytes, to which you refer, occurred during the terminal illness when presumably the leukemia was further advanced than it had been previously. Up to that time he had at most about 25 or 30 per cent granulocytes in the peripheral blood. It is notable that when he had meningococcal meningitis, the spinal fluid examined on the second day showed 1,150 cells of which 75 per cent were polymorphonuclear leukocytes. Is there a specific mechanism by which polymorphonuclear leukocytes reach the spinal fluid, even though they are not present in large numbers in the peripheral blood?

DR. CHERNOFF: I cannot answer that question. We have followed one other patient with chronic lymphocytic leukemia who had several bouts of pneumococcal meningitis, and on both occasions she developed a significant polymorphonuclear leukocytic response in the spinal fluid.

DR. GLASER: Do you have any ideas about this phenomenon, Dr. Harrington?

DR. HARRINGTON: One might suppose that polymorphonuclear leukocytes, being attracted to the site of acute bacterial infection, get across the blood-brain barrier into the spinal fluid where they tend to concentrate. On the other hand, lymphocytes, not being attracted in the same way, are not present.

DR. GLASER: In other words, you would explain it on the basis of a selective response.

DR. HARRINGTON: Yes, but I emphasize that my explanation is a postulate only.

DR. GLASER: We have already pointed out that when this patient had meningococcal meningitis the first specimen of spinal fluid examined was free of both bacteria and cells although on culture meningococci were recovered. Dr. Harford saw the patient in consultation soon after the first lumbar puncture had been done, and predicted that some hours later cells would indeed be found in the spinal fluid. He based this prediction on the hypothesis that the first tap was done so early in the course of the disease that there had been insufficient time for a cellular response. Dr. Harford, is such a sequence frequent in meningitis or is it related to the fact that this man had leukemia?

DR. CARL G. HARFORD: I don't think it is related to the concomitant existence of leukemia. It is not uncommon, especially in pneumococcal meningitis, to find organisms in spinal fluid in the absence of cells. It is possible, however, that if the lumbar puncture is done particularly early, one may see few or no bacteria and no cells such as was the case here. There is a difference of opinion in regard to the pathogenesis of meningitis. One of the attractive explanations, I think, is that spinal fluid being an excellent culture media, bacteria first merely grow in it and only subsequently set up an inflammatory reaction to which the polymorphonuclear leukocytes respond.

DR. GLASER: In this particular instance wasn't the meningitis almost certainly secondary to meningococcemia?

DR. HARFORD: Yes, I would agree. It should also be pointed out that although the spinal fluid did contain bacteria, the spinal fluid sugar level was normal. That observation is compatible with Dr. Goldring's work in our laboratory.[1] He was able to show in dogs that the low spinal fluid sugar in bacterial meningitis could not be attributed to the utilization of sugar by bacteria *per se*.

DR. GLASER: This patient responded excellently to therapy with penicillin and sulfadiazine, although the level of sulfadiazine achieved was relatively low, being of the order of 7 mg. per cent. Dr. Hunter, would you comment on the treatment of meningococcal meningitis, and particularly on the efficacy of penicillin alone in comparison with a sulfonamide?

[1] GOLDRING, S. and HARFORD, C. G. Effect of leucocytes and bacteria on glucose content of the cerebrospinal fluid in meningitis. *Proc. Soc. Exper. Biol. & Med.*, 75: 669–672, 1950.

DR. THOMAS H. HUNTER: Until recently I considered meningococcal meningitis one of the few remaining diseases in the treatment of which sulfonamides should be used. A recent paper, however, by Drs. Lepper and Dowling reports on the use of a sulfonamide in comparison with penicillin in the treatment of patients with meningococcal meningitis.[2] Previously they had shown that very large doses of penicillin given parenterally constituted an effective form of treatment in pneumococcal meningitis. In their most recent study in which about forty patients were treated, they had as good results with large doses of parenteral penicillin alone as they did with the sulfonamide. Using a dose of 1,000,000 units of penicillin every two hours they had only one fatality in forty patients so treated, and that patient died within one hour after the initial injection of penicillin. It should be pointed out that in their study fulminating cases were eliminated from both series on the premise that such patients were so desperately ill that it was unjustified to withhold anything that might be of benefit. Unfortunately, even with combination therapy, none of the patients in the latter group recovered. This type of patient still presents a very difficult problem for the clinician. It does, however, appear that in all but the most severe cases of meningococcal meningitis very large doses of penicillin are probably as effective as a sulfonamide.

DR. GLASER: Would you be willing to use penicillin only in the treatment of the next patient you see with meningococcal meningitis?

DR. HUNTER: Yes, I would.

DR. ATKINS: Our patient also received choramphenicol, which was begun at the time he first entered the hospital, before the result of the spinal fluid culture was known.

DR. GLASER: Most of us would agree that chloramphenicol would not now be the drug of choice for meningococcal infections, but it is certainly understandable that you used it before you knew the nature of the patient's infection. It is still the drug of choice in typhoid fever, and that was one of the diagnoses considered when the patient was admitted.

DR. HARFORD: Chloramphenicol reaches the spinal fluid in good concentration and has been used in meningococcal meningitis with good results. This patient was treated at a time prior to the appearance of reports of bone marrow aplasia due to chloramphenicol. Since these reports have come out we would not employ the agent for meningococcal infection.

DR. GLASER: Let us continue now with the discussion of the patient's subsequent course. We find that he entered the hospital for the third time because of thrombophlebitis and cellulitis which responded quite satisfactorily to penicillin and streptomycin therapy. Here again was an instance in which the outlook might have been significantly different had not antibiotic therapy been available. It was on this admission that the patient was first found to have thrombocytopenia, and because of this finding anticoagulant therapy was not instituted. Dr. Harrington, you were then attending on the ward, and I presume you agreed that anticoagulant therapy should not be used.

DR. HARRINGTON: Yes, I did.

DR. GLASER: Did the appearance of thrombocytopenia suggest that the disease process was moving along at a more rapid rate and had a less good prognosis?

DR. HARRINGTON: Yes, I think so. The patient showed signs of bone marrow depression in general. I don't remember what his reticulocyte count was on that admission, but most patients with chronic lymphocytic leukemia who develop thrombocytopenia do so on the basis of bone marrow replacement. Concomitantly they exhibit anemia, reticulocytopenia and, of course, marked granulocytopenia. There are a few patients, however, who develop hemolytic anemia and thrombocytopenia on the basis of splenic overactivity. In these cases, splenectomy may be extremely helpful. For this reason, the reticulocyte count is most important in determining the management at this stage.

DR. GLASER: We come now to the patient's terminal illness. It has been mentioned that he came to the Emergency Room with signs of pulmonary infection, and was advised to enter the hospital. He refused to do so, and as an alternative, was given antibiotic therapy and instructed to return daily to the clinic for further treatment. Although he agreed to do so he did not keep his appointments, and he probably received only two injections of repository penicillin prior to his entrance into the hospital on October 1st. He was acutely ill, his temperature was 40°C. and he had signs of

[2] LEPPER, M. H., DOWLING, H. F., WEHRLE, P. F., BLATT, N. H., SPIES, H. W. and BROWN, M. Meningococcic meningitis: treatment with large doses of penicillin compared to treatment with gantrisin. *J. Lab. & Clin. Med.*, 40: 891, 1952.

consolidation in the right lung. His white count was 20,800 and it was at this time that the granulocytic response in the peripheral blood was better than it had ever been during his entire course. Dr. Wilson, will you tell us about the chest films during the final illness.

DR. WILSON: A film was taken when the patient first came to the Emergency Room on September 25th. The findings were consistent with pneumonitis in the right middle lobe; the lower lobe appeared clear. The cardiac silhouette and mediastinal shadows had not changed significantly. On October 1st, the day he entered the hospital, another chest x-ray was taken. A striking change had occurred which seemed almost incredible in view of the short time which had elapsed since the previous x-ray. There was an increase in the amount of infiltration in the middle lobe, and now there was involvement of the lower lobe on the right. An extraordinary multiloculated peripheral plaque-like arrangement of fluid or semi-solid material was seen, presumably in the pleural cavity. In the lateral projection it looked like a discrete lobulated mass. Another new finding was the presence of a large oval mass in the mediastinum, along the transverse aortic arch, which could likewise be visualized in the lateral projection. Three days later films again revealed the area of loculated fluid or plaques in the pleural cavity, the huge mediastinal mass, and right lower and middle lobe infiltration. I might say in passing that although the appearance of the pulmonary infiltration was entirely compatible with an inflammatory lesion, the pleural involvement, which we have described as possibly due to loculated fluid, was also strongly reminiscent of the pleural plaques seen with lymphosarcoma.

DR. GLASER: When the patient was admitted to the ward the diagnosis of the staff was pneumonia with probable pleural effusion. Several thoracenteses were attempted but no fluid was obtained. He was given penicillin and streptomycin and then, because proteus organisms were recovered from the sputum, terramycin was added. Despite this treatment the patient did not do well. His temperature shortly after entry rose to 41.0°C. It then gradually fell to 39°C. on the fourth or fifth day at which time he became disoriented and developed meningeal signs. A lumbar puncture was performed and the spinal fluid revealed 15,000 cells, almost all of them polymorphonuclear leukocytes. The bacteriologic findings were at variance. The smear was reported as showing gram-positive cocci, but on culture both the spinal fluid and the blood were positive for Alcaligenes fecalis. Dr. Galambos, there was no doubt in your mind that the organisms were gram-positive.

DR. JOHN T. GALAMBOS: I felt certain they were.

DR. GLASER: Dr. Harford, under what circumstances do gram-negative organisms appear to be gram-positive or vice versa?

DR. HARFORD: It is often not realized that the gram stain is really a rather tricky one. For example, one may not use enough iodine or may decolorize too long, and unless there are known gram-positive and gram-negative controls on the same slide the results may be open to question. Further, under certain conditions, some bacilli may appear to be coccoid.

DR. GLASER: It is also true, is it not, that antibiotic therapy may alter the gram-staining properties of some bacteria?

DR. HARFORD: Yes, that is important. Further, certain gram-positive bacteria contain autolytic enzymes which cause them to become gram-negative. The pneumococcus is a good example.

DR. GLASER: On the basis of the information available, how do you evaluate the findings?

DR. HARFORD: I would pay much more attention to the culture than to the smear.

DR. GLASER: I would agree with you. That leads to another interesting question, namely, how often does Alcaligenes fecalis cause human disease? Dr. Hunter, would you answer that?

DR. HUNTER: It is certainly a rare cause of disease in man. In a series of urinary tract infections with coliform organisms, only five of two hundred were due to Alcaligenes fecalis. Similarly in a large group of patients treated with streptomycin in the "early days" of that antibiotic when it was used for all types of gram-negative infections, there were only five cases in Keefer's whole series due to Alcaligenes fecalis.

DR. GLASER: What is known about the response of Alcaligenes fecalis to the particular antibiotics which were used in this instance—penicillin, streptomycin and terramycin?

DR. HUNTER: There is very little information available, particularly in regard to the effect of combinations on the organism. A certain number of strains are sensitive to streptomycin.

DR. GLASER: Dr. Bukantz, this patient had pneumonia and was reported to have gram-

positive cocci in the spinal fluid. Should we consider pneumococcal meningitis?

DR. SAMUEL C. BUKANTZ: I don't think so. I agree with Dr. Harford that much more attention should be paid to the culture than to the smear.

DR. GLASER: Dr. Galambos, was a methylene blue stain used in order to get a better idea of the morphology of the organism.

DR. GALAMBOS: Unfortunately not.

DR. GLASER: A significant point against pneumococcal meningitis is that pneumococci are very sensitive to penicillin, and with the dosage of that antibiotic which the patient received, a pneumococcal infection should have been easily controlled. Also, Dr. Wilson has indicated that although the roentgenologic findings were suggestive of pulmonary infection, the pleural lesions may have been due to leukemic infiltration and the lung lesion may also have arisen on the same basis.

DR. HUNTER: Perhaps the patient had a mixed infection originally. This situation is one in which such a sequence of events would not be improbable. If he had had a mixed infection with pneumococcus and a gram-negative organism, the pneumococcus would have been killed off, leaving the other organism to take over.

DR. GLASER: In summary, it seems clear that this patient had chronic lymphocytic leukemia, and that his terminal illness was bacterial meningitis, most likely due to the gram-negative rod, Alcaligenes fecalis. It is possible that he originally had a pneumococcal infection in the lung which responded to therapy, and that subsequently the gram-negative organism became dominant.

DR. HUNTER: Dr. Glaser, how do you explain the large mediastinal mass which appeared in such a short period of time.

DR. GLASER: I think it most likely represented enlarged lymph nodes. Do you have something else in mind?

DR. HUNTER: One should also consider the possibility of an abscess, I think.

DR. WILSON: The mediastinal and pleural involvement taken together suggest to me that both were due to the neoplastic process.

Clinical Diagnoses: Chronic lymphocytic leukemia; meningitis due to Alcaligenes fecalis.

PATHOLOGIC DISCUSSION

DR. CHARLES P. CARSON: External examination was not remarkable except for some enlargement of the axillary, cervical and inguinal lymph nodes. The left pleural cavity contained 200 ml. of clear fluid, and the right, 70 ml. The pleura of the right lung was attached by fine, fibrinous adhesions to the thoracic wall. Both lungs were congested and edematous. The pericardial sac was thickened and contained 240 ml. of fluid. A fibrinous exudate of moderate thickness covered the epicardium. The heart was enlarged to 450 gm. but was otherwise essentially unremarkable. In the peritoneal cavity there were about 70 ml. of fluid. The spleen was enlarged and weighed 480 gm. The surface was pale and wrinkled, and on section the stroma was soft and the follicles clearly discernible. The liver was also enlarged to 2,600 gm. The usual liver architecture was altered by many small yellowish streaks about the periphery of the lobules. All the periaortic, portahepatic and mesenteric lymph nodes were markedly enlarged, firm and hemorrhagic. There were several conglomerations of retroperitoneal nodes that projected into the abdominal cavity as pedunculated masses up to 12 cm. in diameter. Both kidneys weighed about half again the normal weight. The surfaces were pale and the cortices were yellow and almost homogeneous. The vertebral and sternal bone marrow were red and soft, while the femoral marrow was grossly fatty and yellow. Examination of the brain revealed no grossly discernible abnormalities.

DR. DAVID E. SMITH: The rather characteristic enlargement of the liver, spleen, kidneys and lymph nodes was compatible with the diagnosis of chronic lymphoid leukemia. However, the lack of obvious hyperplasia of the femoral marrow, and the tremendous enlargement of retroperitoneal and mediastinal lymph nodes due to recent hemorrhage were somewhat atypical findings. The gross appearance of the brain, despite the distinct history of meningitis on two occasions, was remarkably normal.

Figure 1 illustrates the condition of the vertebral bone marrow and is rather unusual for a specimen from a case of chronic lymphoid leukemia. The bone marrow is far from totally replaced by leukemic cells. The center of the field is occupied by a nodule of lymphocytes, but there are also many obvious megakaryocytes and fat cells in other parts of the illustration. The cells between these fat cells are often of the myeloid series and of normal mature appearance. Figure 2 is a higher magnification of an area from the femoral bone marrow.

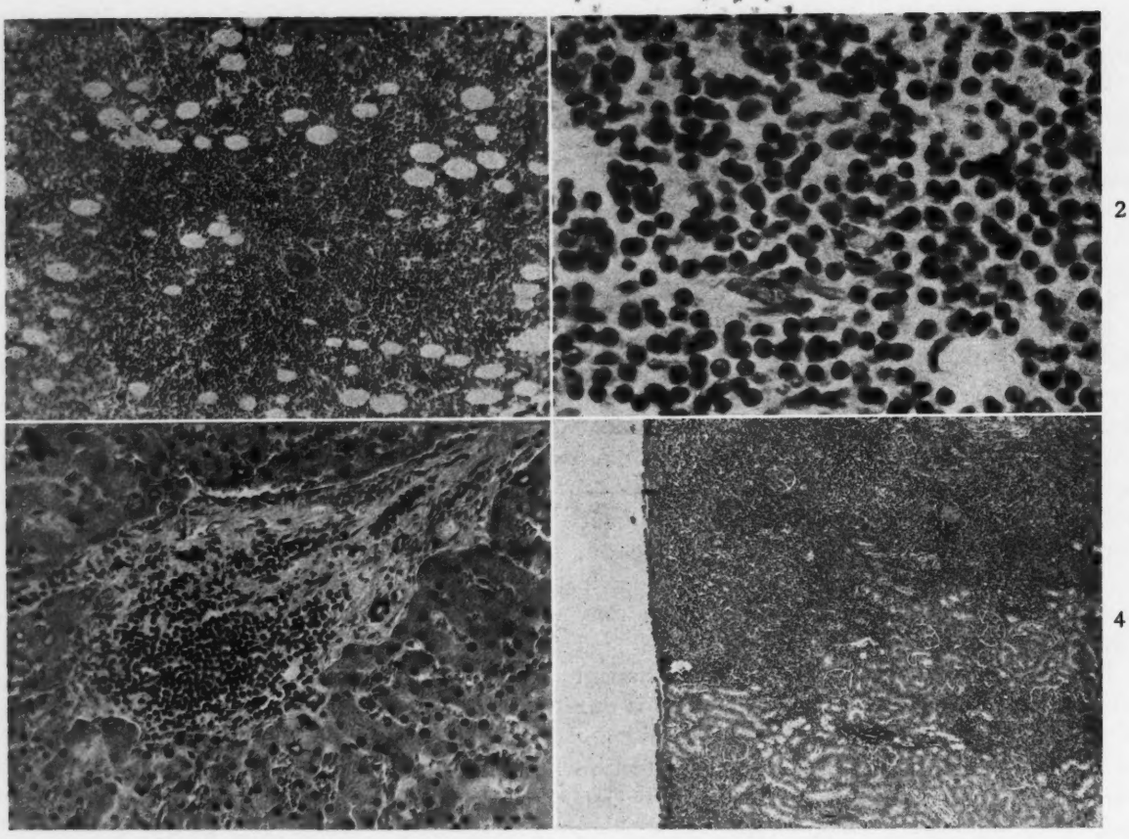

FIG. 1. Vertebral bone marrow in chronic lymphoid leukemia with persistence of many megakaryocytes and myeloid elements with only moderate replacement of fat cells.

FIG. 2. A nodule of mature lymphocytes, typical of chronic lymphoid leukemia, from the femoral bone marrow. This specimen of bone marrow was grossly fatty.

FIG. 3. Section of the liver which was remarkable for the scanty leukemic infiltration despite the increase in weight by 1,000 gm.

FIG. 4. Typical infiltration of chronic lymphoid leukemia in the kidney.

There is a large amount of fat in this specimen of bone marrow, but there are also definite nodules of cells such as those illustrated which are typical lymphocytes. Lymphoid leukemia does not infiltrate the bone marrow as completely and uniformly in many cases as does chronic myeloid leukemia, and in this patient at the time of his death there was only moderate infiltration of the bone marrow by the leukemic cells. It was probably the persistence of normal myeloid tissue that accounted for the rather dramatic reappearance of polymorphonuclear leukocytes in this patient's blood whenever he had an infection, particularly as during his terminal illness. Sections of various lymph nodes showed a total replacement of the normal architecture of those nodes by a diffuse infiltration with lymphocytes. There were, in addition, in the retroperitoneal and mediastinal lymph nodes tremendous amounts of recent hemorrhage that was probably responsible for an acute increase in the size of these nodes.

Sections of the liver (Fig. 3) show remarkably little infiltration by leukemic cells despite the gain of almost 1,000 gm. in the weight of this organ. The cause of the enlargement of the liver in patients such as this is often not apparent microscopically and can hardly be attributed to the volume of infiltrating leukemic cells. The kidney, on the other hand, as illustrated in Figure 4, showed a very considerable infiltration typical of chronic lymphoid leukemia. The spleen was also quite extensively infiltrated.

The brain contained evidence of leukemia that can be seen in Figure 5. This consisted of small perivascular collections of lymphoid cells unassociated with other lesions. None of these formed very significant masses and were strictly microscopic findings. Despite their grossly normal appearance the meninges con-

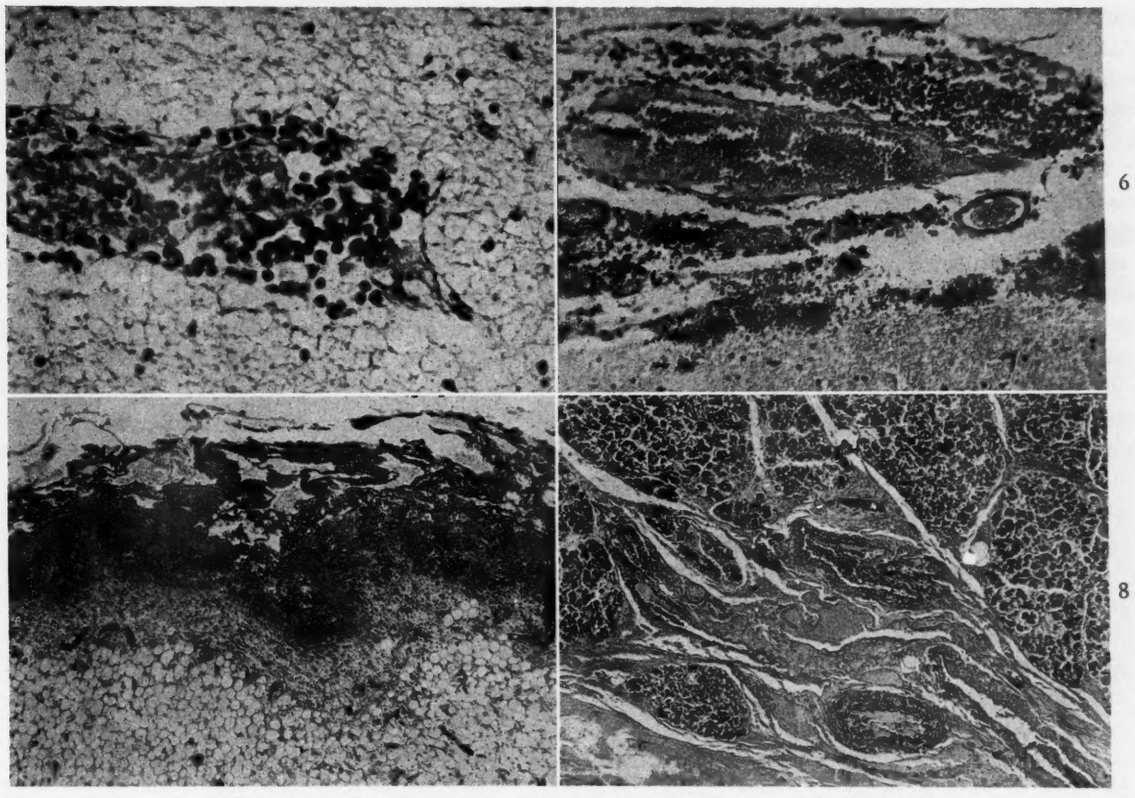

FIG. 5. Perivascular infiltration of lymphocytes in the brain, a manifestation of the leukemia.

FIG. 6. Acute purulent leptomeningitis; the cells are largely polymorphonuclear leukocytes despite the established diagnosis of chronic lymphoid leukemia.

FIG. 7. Partially organized, serofibrinous pericarditis with no obvious anatomic, clinical or bacteriologic cause. A similar type of change involved the right pleural cavity.

FIG. 8. The pancreas, with remarkable amounts of thick, protein-rich interstitial fluid between the lobules. With the pericarditis and pleurisy, this edema appears to indicate an increased permeability of blood vessels.

tain a definite infiltration of leukocytes as is shown in Figure 6. The cells are largely polymorphonuclear neutrophils. This seems compatible with the large numbers of cells of this series that were seen in the bone marrow of this patient. Despite this evidence of a normal type of cellular response to inflammation, however, it cannot be assumed that this man responded normally to infections. Obviously the history of recurrent infections strongly suggests abnormal susceptibility.

The status of the serous membranes points to another disorder in this patient. Figure 7 is from a slide of the pericardium. There is a definite pericarditis with broad bands of fibrin on the surface, and beneath that a zone of organization. There are practically no inflammatory cells, and certainly no leukemic infiltrates in this membrane. No evidence of any of the usual causes of pericarditis is obvious. There is nothing indicative of infection or of uremia, and there is no destruction of the membrane by the leukemic disease. It seems possible, therefore, that this sterile, serofibrinous pericarditis indicates an alteration in the permeability of this patient's capillary membranes. This change perhaps accompanied the thrombocytopenia, or was a reflection of the status of the serum proteins which may have been abnormal despite the recorded normal results in one examination during life. The pleura of the right thoracic cavity was covered by an essentially similar sterile, organizing, serofibrinous pleurisy. The underlying lung was normal in both gross and microscopic appearance and showed no evidence of parenchymal changes such as pneumonia. Figure 8 is of another lesion that also might well indicate the presence of increased permeability of the small vessels. It shows a rather remarkable degree of interstitial edema in the pancreas. Again, there is no evidence of inflammation or leukemic infiltration in this

particular locality. Conceivably, the increase in the size of the liver without extensive cellular infiltration might also be on the basis of a morphologically imperceptible imbibition of fluid.

Postmortem cultures of the blood and the meninges were sterile, and bacterial stains of appropriate sections showed no recognizable organisms. No further information can be given as to the etiology of the meningitis than that indicated by the clinical record. Apparently it was completely arrested by the antibiotics.

In summary, the morphologic findings indicate that this patient had chronic lymphoid leukemia that was well compensated from an anatomic standpoint. His resistance to infections was lowered, however, and for some reason there was extensive exudation of fluid into various tissues and hemorrhage into many lymph nodes. The combination of infection, edema and hemorrhage seem to have been responsible for most of the puzzling clinical features of this case.

Anatomic Diagnoses: Chronic lymphoid leukemia; acute purulent meningitis; partially organized serofibrinous pericarditis and pleurisy, right; congestion and edema of the lungs; hydrothorax, left; interstitial edema of the pancreas.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

Research Society Abstracts

American Federation for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE NATIONAL MEETING IN ATLANTIC CITY, NEW JERSEY, MAY 4, 1952

ELECTROCARDIOGRAPHIC CHANGES IN POLIOMYELITIS: ANALYSIS OF 472 PATIENTS. *W. H. Ames, M.D., L. E. January, M.D. and P. Wheeler, M.D. (introduced by R. D. Eckhardt, M.D.).* (From the Cardiovascular Lab., State Univ. of Iowa College of Medicine, Iowa City, Ia.)

An extensive electrocardiographic survey in patients with poliomyelitis was undertaken to evaluate the electrocardiogram as an aid in the clinical recognition of myocarditis, a complication of poliomyelitis found usually at autopsy. Six hundred eighty-seven electrocardiograms, consisting of 12 leads, were made on 472 patients hospitalized during one epidemic. Serial electrocardiograms were obtained on fifty-four respirator patients. Forty-two tracings were available for analysis from twenty-two deaths. Comparison of the electrocardiographic and pathologic material was possible in thirteen autopsied patients. A statistical analysis was made of the incidence of electrocardiographic abnormalities with particular attention directed to the relationships of the Q-T interval and myocardial disease. Abnormalities included prolongation of the Q-T interval, rhythm disturbances and RS-T segment and T wave changes. Results were correlated with age and sex distribution, severity of the disease, type of involvement and presence of fever. Prolongation of the Q-T interval was the predominant abnormality, being present in 14.6 per cent of all cases and 40.4 per cent of the bulbar type. Lack of specific correlation between the autopsy and electrocardiographic findings suggests that the electrocardiographic abnormalities may represent physiologic rather than anatomic disturbance.

VALIDITY OF VECTORCARDIOGRAPHIC TRANSLATION OF PRECORDIAL ELECTROCARDIOGRAPHIC PATTERNS. *R. L. Andreassen, M.D. and L. A. Soloff, M.D.* (From the Dept. of Medicine, Temple Univ. Hospital and School of Medicine, Phila., Pa.)

An individual with myocardial infarction presented an electrocardiographic pattern of inversion T_{v4} and$_5$ with upright $T_{v1,2,3,6}$. Complete exploration of the trunk by Grant's method disclosed that these inversions were not isolated but were part of a bizarre asymmetry in the distribution of the electrical field of the T force. Because T wave negativity, if present, usually occurs on either end of the conventional series of precordial leads and because "isolated" T wave negativity is attributed to the mechanical impact of cardiac muscle which may change with myocardial dysfunction or disease, a study was begun of the exploration of the trunk with V leads placed both anteriorly and posteriorly at close intervals in a uniform grid pattern. Twenty-seven subjects were studied. Of these nineteen had T wave transition points that within narrow limits could be predicted from the precordial pattern. The other eight had transitional zones that were not predictable. Five had a moderate degree of asymmetry and the other three had bizarre transition zones that had almost no resemblance to the predicted zones. The theoretic and practical significance of this study will be discussed.

HEMODYNAMIC EFFECTS OF A HYDRAZINOPHTHALAZINE COMPOUND (APRESOLINE) IN HYPERTENSIVE COMPLICATIONS OF PREGNANCY. *N. S. Assali, M.D., W. W. Baird, M.D.,* R. A. Douglass, M.D.* and E. L. Tioseco, M.D.** (From the Dept. of Obstetrics, Cincinnati General Hospital and Univ. of Cincinnati College of Medicine, Cincinnati, O.)

Some hemodynamic effects of apresoline® were investigated in the following groups of patients: (1) ten normotensive pregnant, (2) sixteen with toxemia of pregnancy and (3) thirteen with essential hypertension associated with pregnancy. Sixty-two tests were performed on these thirty-nine patients, each test con-

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sisting of an acute intravenous dose of 20 to 40 mg. (average 30 mg.). A single intravenous injection produced a mean 6 per cent fall in the diastolic blood pressure of the normotensive group. The systolic was practically unchanged. In the toxemic group the same dose evoked a mean 26 per cent systolic and 43 per cent diastolic fall lasting from three to twenty-two hours. In the essential hypertensive group the intravenous dose resulted in a mean 11 per cent systolic and 19 per cent diastolic fall, lasting from one to five hours. In groups 2 and 3, at the height of vasodepression, tachycardia was invariably present; cold pressor test was not totally abolished; cardiac output and cardiac force (ballistocardiograph) were increased; skin temperature of the upper extremities rose more markedly than that of the lower extremities. The renal blood flow was increased but the glomerular filtration rate was diminished; the renal vascular resistance (Gomez formula) was reduced. It is concluded that although the mechanism of action of apresoline is obscure, its hemodynamic effects are different from those produced by ganglionic and adrenergic blocking agents. The drug is particularly indicated in the treatment of toxemia of pregnancy.

HEMODYNAMIC PROPERTIES OF A THIOPHANIUM COMPOUND (RO 2-2222) IN HUMAN SUBJECTS. *N. S. Assali, M.D. and R. A. Douglass, Jr., M.D.** (From the Dept. of Obstetrics, Cincinnati General Hospital and Univ. of Cincinnati College of Medicine, Cincinnati, O.)

It has been shown in animals that Ro 2-2222 has a similar but more potent vasodepressor and ganglionic blocking action than tetraethylammonium ion (TEA). Studies on the hemodynamic effects of this compound were performed on fifty-four patients (five normotensive non-pregnant, twenty-six normotensive pregnant, ten with toxemia of pregnancy and thirteen with essential hypertension associated with pregnancy). Acute intravenous injections of 0.1 to 0.2 mg./kg. resulted in brief but marked fall in blood pressure of normotensive pregnant and essential hypertensive subjects. Pulse rate increased. The effect in normotensive non-pregnant and toxemic patients was negligible. Intravenous infusion of 4 to 36 mg./minute with 5 per cent glucose and water resulted in average fall of 37 per cent systolic and 44 per cent diastolic blood pressure in normotensive pregnant subjects and 32 per cent/49 per cent in essential hypertensive patients, effective for as long as the intravenous drip was allowed to run. Cumulative effect was rare. In toxemia and normotensive non-pregnant subjects blood pressure fall was much less marked. At the height of hypotension the cold pressor test was usually abolished; postural hypotension was present; cardiac output was diminished; skin temperature of the lower extremities was markedly increased but that of the upper extremities was practically unchanged. Urine flow, glomerular filtration rate and renal plasma flow were reduced. Renal vascular resistance was increased. It is concluded that in human pregnant subjects Ro 2-2222 has autonomic blocking and vasodepressor action similar to TEAC or selective spinal anesthesia. It is effective in reducing blood pressure in cases with an increase in neurogenic tone.

MINOR RESPIRATORY DISEASES; STUDIES OF MR-4 VIRUS DISEASE IN HUMAN VOLUNTEERS. *L. T. Atlas, M.D.* (From the Dept. of Medicine, Harvard Medical School and Peter Bent Brigham Hospital, Boston, Mass.)

Nasal washings were collected from a donor early after onset of respiratory symptoms. His nasal washings and nasal washings from volunteers infected by his secretions were inoculated intranasally into sixty-four human volunteers kept in isolation. A consistent and specific disease entity recapitulating the signs and symptoms of the donor was produced in volunteers. An equal number of controls had no such disease. The signs and symptoms responsible for the observers' subjective judgment of severity of disease or no disease were determined by statistical analysis of the recorded data. All the thirty-two men considered as definitely sick had a profuse running nose after three to five days' incubation time. In addition sneezing, conjunctivitis, headache and irritated throat were often present. This illness differed from that produced by MR-1 and MR-3 viruses but was similar clinically to MR-2 disease. However, unlike MR-2 virus this filtrable agent produced resistance to homologous reinfection for at least one month. MR-4 disease did not prevent heterologous infection by MR-1 or MR-3 viruses. The addition of lyophilized skim milk to an inoculum of known infectivity enhanced the incidence and severity of disease.

EFFECTS OF MILD AND SEVERE ALCOHOLIC INTOXICATION ON CEREBRAL BLOOD FLOW AND METABOLISM. *L. L. Battery, M.D.,* A. Heyman, M.D. and J. L. Patterson, Jr., M.D.** (From the Emory Univ. School of Medicine, Atlanta, Ga.)

The cerebral circulation (CBF) and metabolism ($CMRO_2$) were studied by the nitrous oxide method in fourteen convalescent subjects before and after intravenous infusions of varying amounts of 5 to 10 per cent ethyl alcohol. Blood alcohol levels of these patients ranged from 15 to 137 mg. per cent and produced symptoms of mild intoxication. No significant change in cerebral blood flow or metabolism was observed. Similar studies were performed on six patients during the comatose stage of severe self-induced alcohol intoxication and following recovery. All patients had evidence of severe intoxication confirmed by blood alcohol levels. During alcoholic coma these patients had a slight increase in cerebral blood flow with a mean value of 57 cc. and a marked reduction in $CMRO_2$ with a mean value of 2.2 cc./100 gm. brain/minute. Following recovery the CBF and $CMRO_2$ became practically normal with mean values of 47 cc. and 3.3 cc./100 gm./minute, respectively. These studies indicate that mild alcoholic intoxication, rapidly produced, has little effect on the cerebral circulation or metabolism. Severe alcoholic intoxication, however, is usually associated with cerebral vasodilatation and marked depression of cerebral metabolism. The late mental changes of chronic alcoholism may be related in part to repeated episodes of depression of brain metabolism caused by alcohol.

CLINICAL AND LABORATORY OBSERVATIONS IN RHEUMATIC DISEASE FOLLOWING HIGH DOSAGE CORTISONE THERAPY. *T. B. Bayles, M.D., F. L. Colpoys, Jr., M.D.,* P. Fremont-Smith, M.D.,* B. C. Ferguson, M.D.* and Emil Paige, M.D.** (From the Harvard Medical School, Robert Breck Brigham and Peter Bent Brigham Hospital, Boston, Mass.)

Since a few patients remained well after intensive adrenocorticotropic hormone therapy, we have attempted to produce prolonged or permanent remissions in rheumatic disease. Twenty-three patients have been given twenty-six courses of high dosage cortisone therapy for from fourteen to twenty-eight days. All adults received 500 mg. per day and children, 300 to 400 mg. per day. Fourteen adult rheumatoid arthritics received sixteen courses of treatment, five by mouth and eleven parenterally. Four patients with juvenile rheumatoid arthritis received five courses of treatment, two by mouth and three parenterally. Three patients with disseminated lupus erythematosus were treated parenterally. Adult rheumatoid arthritics, when treated per orum, relapsed within three weeks while those parenterally treated averaged sixty days of remission before relapsing; one remained well. Three patients with lupus erythematosus disseminatus relapsed in four weeks but two remained improved compared to pretreatment status. In chronic rheumatic fever one of the two patients has been in remission 13 months. All juvenile rheumatoid arthritis patients relapsed in four weeks. There is no laboratory or clinical evidence that high dosage cortisone given parenterally persists beyond the first twenty-one days of the remission. Immunologic, blood lipid and partitioned protein studies will be reported.

INTRAMUSCULAR USE OF PRONESTYL (PROCAINE AMIDE): BLOOD LEVELS IN NORMAL SUBJECTS AND THOSE WITH CONGESTIVE HEART FAILURE AND RENAL INSUFFICIENCY. *Samuel Bellet, M.D., Stanley E. Zeeman, M.D.* and Stanton A. Hirsh, M.D.** (From the Philadelphia General Hospital and the Robinette Foundation, Univ. of Pennsylvania, Phila., Pa.)

The therapeutic range, relative efficacy and serum levels of intramuscular preparations of pronestyl® were determined after oral and intravenous administration. Sixty-five subjects were studied: nineteen normal; four with congestive heart failure; seven with congestive heart failure and renal insufficiency; six with primary renal insufficiency and twenty-nine with various ectopic rhythms with and without heart failure and renal insufficiency. Serum levels indicated that absorption by the intramuscular route is quite satisfactory. An appreciable level was observed within five minutes, peak levels usually at fifteen minutes to one hour, a significant level was still observed at six hours, after which the serum levels declined slowly. Following similar doses (0.5 to 1.0 gm.) of pronestyl by the oral and intramuscular route in patients with congestive heart failure and renal insufficiency, the blood level attained was significantly higher and the return to normal considerably delayed. This point is of considerable

importance when multiple doses are given to such patients with ectopic rhythms because the delay in elimination should be considered in continued administration to avoid toxic levels. Intramuscular administration in the treatment of arrhythmias was as efficacious as oral or intravenous administration. When given intramuscularly, however, pronestyl had a more rapid action than by the oral route and a slower action than by the intravenous route. Toxic effects were generally mild and compare favorably to those following the oral route of administration. The severe hypotension which occasionally follows intravenous administration was not seen. It is believed that the intramuscular method is relatively safe and is in most instances preferred for the parenteral administration of this drug.

EFFECTS OF ORAL 688-A (N-PHENOXY-ISOPROPYL-N-BENZYL-β-CHLORETHYLAMINE HYDROCHLORIDE) ON THE BLOOD PRESSURE OF HYPERTENSIVE SUBJECTS. *C. T. Bello, M.D. and L. A. Soloff, M.D.* (*introduced by S. H. Lorber, M.D.*). (From the Temple Univ. Hospital and School of Medicine, Phila., Pa.)

Six individuals with hypertension of the essential type of years duration were hospitalized at Temple University Hospital to evaluate the effects of oral 688-A. After the blood pressures were demonstrated to be stable and following placebo medication, 688-A was given orally to these subjects for seven to ten days. After testing the individuals for sensitivity with small doses the dosage was raised from 20 to 120 mg. a day to as much as 2,000 mg. a day. This dosage was maintained for five days. Blood pressure readings were recorded every four hours. Physical examinations were made daily or more frequently and all symptoms were recorded. The drug uniformly failed to reduce blood pressure or to produce symptoms suggestive of absorption of the drug. To test absorption the pressor effects of epinephrine were studied before, during and after exhibition of 688-A therapy. In this small series oral 688-A failed to reduce blood pressure in the hypertensive subject or to give any evidence of absorption.

EFFECTS OF ORALLY ADMINISTERED HEXAMETHONIUM BITARTRATE ON HYPERTENSION. *C. T. Bello, M.D., W. Steiger, M.D., J. Doane, M.D. and L. Turner, M.D.* (*introduced by S. H. Lorber, M.D.*). (From the Temple Univ. Hospital and School of Medicine, Phila., Pa.)

Fifteen patients from the hypertensive clinic of Temple University Hospital were selected for this study. These patients were considered a representative cross section of types of essential hypertension. All patients in this study attended the hypertensive clinic for many months. In addition, a control period with placebo therapy was instituted prior to the oral administration of hexamethonium bitartrate therapy. The hexamethonium bitartrate salt was administered for six weeks in daily oral divided doses ranging from 1 to 6 gm. Blood pressure readings were taken at weekly intervals under controlled conditions. Following the course of hexamethonium bitartrate these patients were again placed on placebo therapy. Blood pressure readings and symptoms, both subjective and objective, were recorded prior to, during and after hexamethonium bitartrate therapy. The drug failed to reduce blood pressure or to produce symptoms suggestive of absorption by the oral administration. In several of these patients hexamethonium bitartrate salt was administered intravenously and the signs and symptoms of the ganglionic blocking properties of this drug were demonstrated. The bitartrate salt was selected for this study instead of the bromide salt in order to avoid the sedative effects of the bromide ion and the influence of sedation on the blood pressure of hypertensive individuals.

STUDIES ON INTRAVENOUS WATER DIURESIS AND NICOTINE AND PITRESSIN ANTIDIURESIS IN PATIENTS WITH LIVER DISEASE. *S. H. Bernstein, M.D., G. Ross, M.D., J. Grossman, M.D., L. Leiter, M.D.* and R. E. Weston, M.D.* (From the Medical Division, Montefiore Hospital, New York, N. Y.)

To determine whether patients with liver disease and ascites, on low salt diets, can adequately excrete water under high intravenous water loads, 5 per cent glucose in water solutions were administered intravenously at rates of 15 to 20 ml./minute. Then to compare the degree and duration of pitressin® antidiuresis with the antidiuresis of endogenously released ADH, nicotine salicylate was injected intravenously in 1 to 3 mg. doses at the height of diuresis. When urine flows returned to control levels, pitressin was administered in dosage estimated to produce equivalent antidiuresis. Serum Na, Cl and K concentrations, corresponding urinary electrolyte excretions, creatinine clearance and eosinophil counts were

measured. The urine volumes during water loading were essentially equivalent to the infusion rate in all but two patients. The average time required to attain peak diuresis, ninety minutes, was similar to that previously reported for cirrhotic patients and normal subjects given smaller intravenous water loads. The degree and duration of nicotine antidiuresis were equivalent to those following 10 to 20 milliunits of pitressin. Urinary electrolyte excretion rate did not change significantly, despite decreases in serum concentrations during water loading. Except for slight changes associated with urine flow, creatinine clearances remained constant. These data suggest that tolerance to intravenous water loads in patients with liver disease is unimpaired. The equivalent duration of nicotine and pitressin antidiuresis points to a similar rate of inactivation of antidiuretic substance of endogenous or exogenous origin in cirrhotic patients.

RELATIONSHIP OF PLASMA TIME-CONCENTRATION CURVES TO PLASMA VOLUME, INTERSTITIAL FLUID VOLUME, VASCULAR PERMEABILITY AND RENAL CLEARANCE OF SUBSTANCES CONFINED TO THE EXTRACELLULAR FLUID. *W. R. Best, M.D.* (From the U. S. Army Medical Nutrition Lab., Chicago, Ill.)

The exact contour of time curves describing plasma concentration, interstitial concentration and total quantity in the body following a single intravenous injection of an extracellularly distributed substance were studied through a simple hydraulic analogy. The volume of each body fluid compartment was represented by the cross sectional area of a cylindrical container; the concentration of substance in that compartment by the height of water contained; and the amount of substance present by the volume of water. Vascular permeability and renal clearance were represented by the resistance to water flow in horizontal spouts at the bottom of each container. Assuming a uniform vascular permeability and instantaneous mixing within each compartment, all factors contributing to final concentration curves can be precisely studied with this analogy and translated into the biologic system. Thus changing plasma concentrations are described as the sum of two exponential curves. The characteristics of these curves are intricately related to dose of substance, plasma volume, interstitial volume, vascular permeability and renal clearance. A fixed ratio of plasma to interstitial concentrations is ultimately achieved and is defined by these factors. The hydraulic analogy may be further broadened to consider multiple vascular areas having different permeabilities, as probably occurs *in vivo*.

OXYGEN AND GLUCOSE CONSUMPTION OF THE LIVER IN MAN. *H. R. Bierman, M.D., L. P. White, M.D.,* and K. H. Kelly, M.D.* (From the National Cancer Institute, National Institutes of Health and Univ. of California School of Medicine, San Francisco, Calif.)

Portal venous blood was obtained from thirty patients with cancer by direct transhepatic venepuncture through the intact abdominal wall. The oxygen and glucose content of portal venous blood were compared with simultaneously drawn arterial and hepatic venous blood. The oxygen saturation of portal venous blood averaged 69.7 per cent (range 59.2 to 80.5 per cent) or approximately midway between the hepatic venous 55.1 per cent (range 38.2 to 63.0 per cent) and arterial blood 91.7 per cent (range 87.7 to 96.0 per cent). The glucose content of portal venous blood averaged 17 mg. per cent above the peripheral venous or arterial content in thirteen cases, with a range of 7 to 55 mg. per cent. In six patients the glucose content was equal to or below that of the peripheral venous or arterial blood. In five cases the portal content was greater than that in the hepatic blood, averaging 13 mg. per cent (range 10 to 22 mg. per cent) above the hepatic vein; in four patients there was no significant difference. In two patients the hepatic vein glucose content was greater than that in the portal blood, by 9 mg. per cent and 26 mg. per cent, respectively. By determining hepatic blood flow a differentiation of glucose and oxygen consumption of the portal organs and the liver is now possible. Transhepatic portal venepuncture in man is technically feasible as a bedside procedure with little risk or discomfort and affords a direct clinical approach to the portal venous system.

MOBILITY OF HUMAN PLATELETS IN A MICRO-ELECTROPHORESIS CELL. *F. S. Bigelow, M.D. and J. F. Desforges, M.D.* (From the Thorndike Memorial Lab., Boston City Hospital and the Harvard Medical School, Boston, Mass.)

The surface charge of human platelets has been investigated by microscopic observation of electrophoretic mobility. On application of direct current (5 milliamperes), platelets mi-

grated toward the positive pole of the cell. Platelets, isolated from oxalate-decalcified human whole blood by differential centrifugation, were washed four times and resuspended in imidazole-buffered physiologic saline (pH 7.25). Washed platelets, whether isolated from oxalate-decalcified or native undecalcified whole blood, had identical mobilities, which were unaltered after six hours at 6°C., 27°C. and 37.5°C., or after ten minutes at 56°C. Mobility was reduced after freezing and by insufficient washing. Washed platelets exposed *in vitro* to various agents were rewashed four times and their mobility contrasted with similarly manipulated control platelets. Gelatin exposure decreased mobility but thrombin, thromboplastin, heparin, protamine, trypsin, streptokinase, streptodornase and human fibrinolysin were ineffective. Platelets exposed to prothrombin conversion in recalcified defibrinated normal plasma retained normal mobility. Platelets from patients with hemolytic anemia, paroxysmal nocturnal hemoglobinuria, pernicious anemia, polycythemia, hemophilia, spontaneous fibrinolysis and four instances of idiopathic thrombocytopenia with and without splenectomy, were electrophoretically normal. Reduced platelet mobility occurred in one instance of acute thrombocytopenia with tuberculosis and in a cirrhotic male who had had splenectomy for thrombocytopenia. Platelet mobility during hemorrhage is being investigated.

DIURETIC RESPONSE TO WATER INGESTION IN THE PRESENCE OF ELEVATED SERUM ELECTROLYTE LEVELS AND EXPANDED EXTRACELLULAR FLUID VOLUME. *W. H. Birchard, M.D.,* J. D. Rosenbaum, M.D. and M. B. Strauss, M.D.* (From the Cushing Veterans Administration Hospital, Framingham, Mass.)

Three normal recumbent subjects fasting and thirsting for twelve hours excreted urine at an average rate of 1.1 ml./minute. Following the intravenous infusion in sixty minutes of 1 L. of hypertonic sodium chloride solution (342 mEq./L.) an osmotic diuresis occurred with urine flow increasing to 3.5 ml./minute, and urine electrolyte concentration rising to 568 milliosmols/L. One hour after the infusion was terminated, at a time when urine flow was declining, 1 L. of water was ingested. Approximately seventy-five minutes later a diuresis characteristic of decreased antidiuretic activity commenced, the peak urine flow reading 7.2 ml./minute with electrolyte concentration falling to 205 milli-osmols/L. At this time serum sodium and chloride levels in each subject, although lower than immediately post-infusion, remained higher than the pre-infusion levels. Calculations indicated that extracellular volume was expanded by 0.95 L. at the time of peak diuresis. These data suggest that expanded extracellular volume may inhibit antidiuretic activity even though serum electrolyte values are elevated. An alternate hypothesis is that the fall in serum electrolyte values rather than their absolute magnitude determines the diuretic response.

OXYGEN PRESSURE GRADIENT FROM ALVEOLAR AIR TO ARTERIAL BLOOD IN PATIENTS WITH MITRAL STENOSIS. *S. G. Blount, Jr., M.D.,* M. C. McCord, M.D. and L. L. Anderson, M.D.** (From the Univ. of Colorado School of Medicine, Denver, Colo.)

Pathologic alterations in the alveolar-capillary membrane have been described in patients with mitral stenosis. These findings suggested the possibility of an impediment to oxygen transfer at the alveolar-capillary membrane level in patients with mitral stenosis. Alveolar and arterial oxygen tensions were determined and the alveolar-capillary oxygen pressure gradient calculated in twenty young healthy persons to establish normal values for this altitude. Similar determinations were made and cardiac catheterization performed on fifteen patients with mitral stenosis of varying severity. The mean oxygen pressure gradient across the alveolar-capillary membrane in normal persons was 5.46 mm. Hg at rest and 11.05 mm. Hg following exercise. In contrast, the alveolar-capillary oxygen pressure gradient in patients with mitral stenosis was 12.29 mm. Hg at rest and 16.64 mm. Hg with exercise. The differences in the alveolar-capillary oxygen pressure gradient in these two groups indicate a physiologic counterpart to the known pathologic alterations in the alveolar-capillary membrane in patients with mitral stenosis. The differentiation of the components of the total alveolar-capillary oxygen pressure gradient is considered. The severity of the mitral stenosis, as determined clinically and by cardiac catheterization, is correlated with the alveolar-capillary oxygen pressure gradient.

PAROXYSMAL COLD HEMOGLOBINURIA; RENAL FUNCTION STUDIES DURING AN INDUCED HEMOLYTIC EPISODE. *J. H. Brandt, M.D. and H. C. Lichtman, M.D.* (From the State Univ. of New York, College of Medicine, Brooklyn, N. Y.)

To determine whether renal dynamic changes were produced by homologous hemoglobin (the patient's own hemoglobin) a twenty-five year old female with paroxysmal cold hemoglobinuria and with no primary renal disease was studied. Blood examination showed a positive STS and a positive Donath-Landsteiner test. Red blood cells showed a positive Coombs reaction when first exposed to cold for thirty minutes and a negative Coombs reaction immediately on withdrawal from the body. On the afternoon preceding renal function studies a 200 cc. phlebotomy was done. The blood was collected under sterile conditions into ACD solution and placed in an icebox until the next morning. Following control studies of glomerular filtration and renal plasma flow the patient's refrigerated blood was transfused. Within fifteen minutes gross hemoglobinuria was evident. During the hemolytic episode there was a fall in effective renal plasma flow to 269.5 cc./minute from 412.5 cc./minute and a change in filtration rate from a control of 141.5 cc./minute to 148.5 cc./minute. The filtration fraction rose strikingly from a control of 34 to 55 per cent during the period of hemoglobinuria. Urine flow did not significantly change during the procedure. These results indicate that free circulating hemoglobin induces specific renal hemodynamic changes, whether the source be endogenous from intravascular hemolysis or from an exogenous source as was previously demonstrated in this laboratory using pooled stroma-free hemoglobin solution.

METHOD FOR SIMULTANEOUS MEASUREMENT OF TOTAL EXCHANGEABLE BODY SODIUM AND POTASSIUM IN MAN. *L. Brooks, M.D., A. H. James, M.D., I. S. Edelman, M.D. and F. D. Moore, M.D.** (From the Peter Bent Brigham Hospital, and Harvard Medical School, Boston, Mass.)

The validity of the measurement of total exchangeable sodium by Na^{24} and potassium K^{42} has previously been established. Evidence suggests that reciprocal relationships exist in sodium and potassium metabolism. This paper describes a method for the simultaneous determination of these cations in man.

Separating the isotopic components in equilibration samples following intravenous injection of Na^{24} and K^{42} involves successive cobalt nitrite and alcoholic tartrate precipitation of the serum and the counting of a urine aliquot with and without an aluminum absorber. Complete removal of Na^{24} by this method is demonstrated by serum concentrates from four patients injected with Na^{24} which showed mean counts of 23.1 per minute per 0.5 ml., as compared with a mean background of 23.0 counts per minute. Known mixtures of Na^{24} and K^{42}, prepared as serum concentrates, showed K to Na ratios of 0.17, 0.24 and 0.37, compared with calculated ratios of 0.16, 0.24 and 0.36. Reproducibility was tested in normal subjects by comparing values from combined and single isotope injections at weekly intervals. In three patients the mean difference in exchangeable K was 4.5 per cent (range 0.9 to 6.6 per cent) and in five patients the mean difference in exchangeable Na was 3.5 per cent (range 0.7 to 11.9 per cent).

CORRELATION OF BALLISTOCARDIOGRAM WITH WORK CAPACITY FOR GUIDANCE IN REHABILITATION OF CARDIAC PATIENTS. *H. Brown, M.D.,* S. H. Rinzler, M.D. and J. G. Benton, M.D.* (From the Departments of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center, New York, N. Y.)

During the course of a study of the energy cost of step-walking for a series of forty-five cardiac patients, routine resting ballistocardiograms, using the Dock instrument, were recorded on all patients. The rate of work approximated six times the energy cost of resting metabolism, and the amount of work varied with the duration of performance from one-half to four minutes. Since the ballistocardiographic pattern reflects the mechanical activity of the heart, our data were examined for any correlation existing between the normality of the ballistocardiogram and the amount of work that the patient could perform. Twenty-six patients had normal ballistocardiograms and all were able to complete a moderately strenuous test (1.5 minutes); twenty-one were able to do the three-minute test or better. Of nineteen patients with abnormal ballistocardiograms four could not complete a mild test (one minute) and only four were able to do the three-minute

test or better. Thus the finding of a normal ballistocardiogram in a known cardiac patient appears to be associated with a good to excellent work potentiality. This suggests that the ballistocardiogram may be a useful tool in evaluating the functional or work capacity of a cardiac patient for rehabilitation purposes and vocational guidance.

RADIOACTIVE IODINE CONVERSION RATIO IN THYROID DIAGNOSIS. *B. A. Burrows, M.D., E. S. Dell, M.D.,* J. F. Ross, M.D.* (From the Cushing Veterans Administration Hospital, Framingham, and the Evans Memorial Hospital, Boston, Mass.)

Although the twenty-four hour thyroid uptake of radioiodine is an excellent index of thyroid function in the untreated patient, it agrees less well with the clinical impression and other laboratory tests in patients who have been treated for hyperthyroidism with radioiodine, surgery or antithyroid drugs. This often poses a real problem in evaluating the therapeutic results in such patients; and if they are retreated with radioiodine because of a persistently high uptake, the likelihood of permanent myxedema is increased. We have found that the rate of thyroxin synthesis, as indicated by the ratio of serum protein-bound I^{131} to total serum I^{131} twenty-four hours after an oral dose of I^{131} (conversion ratio), showed good agreement with the state of thyroid function in such patients, as well as in patients who have not received treatment. In 150 patients so studied a conversion ratio below 40 per cent was indicative of normal thyroid function and above 60 per cent of hyperthyroidism. Agreement between the conversion ratio and the thyroid uptake was present in 85 per cent of these patients. When the two tests were at variance, the conversion ratio was generally more reliable.

HEMODYNAMIC PATTERNS IN PRESSOR RESPONSES INDUCED BY STRESSFUL INTERVIEWS. OBSERVATIONS ON HYPERTENSIVE AND NORMOTENSIVE SUBJECTS. *P. V. Cardon, M.D.* and J. T. Flynn, M.D.* (From the New York Hospital, Cornell Medical Center, N. Y.)

The pressor response to stressful interviews has been studied with the aid of the Nickerson low frequency ballistocardiograph in fifty hypertensive patients and twenty normotensive controls. While the ballistocardiograph may not be suitable for comparative determination of cardiac output between individuals or even diurnally, it can reliably reflect relative differences in the same individual observed more or less continuously in a single experiment. The object of the study was to evaluate the respective roles in the pressor response of cardiac output on the one hand and peripheral resistance on the other. In about two-thirds of the patients and most of the control subjects the rise in blood pressure was apparently due entirely to a rise in cardiac output because peripheral resistance fell or failed to change. In the remaining third of the hypertensive subjects peripheral resistance rose while cardiac output remained constant or decreased. The hemodynamic pattern did not correlate with age, sex, level of arterial pressure or the duration of known hypertension. At times the pattern changed in a single interview or from day to day. Typically, an elevation of arterial pressure due mainly to increased cardiac output was encountered at times when the patient displayed relatively overt evidences of emotional disturbance. A rise attributable to increased peripheral resistance occurred when the subjects were relatively restrained and presented a smooth, unruffled exterior. The possible bearing of these observations on the extent and severity of arterial and arteriole damage in brain, heart and kidney is under study.

EFFECT OF TUBERCULOUS INFECTION ON SUCCINIC DEHYDROGENASE ACTIVITY OF GUINEA PIG'S TISSUES. *S. N. Chaudhuri, M.D.* and S. P. Martin, M.D.* (From the Dept. of Medicine, Duke University School of Medicine, Durham, N. C.)

As a part of a study to relate cellular metabolism and resistance to infection, the effect of various types of infection with M. tuberculosis on cellular enzymes was measured. Guinea pigs were used because of marked resistance of the kidney to infection while other organs were susceptible. The organs were homogenized and reduction of tetrazolium was measured colorimetrically. Succinate was the substrate. This system was chosen because of previous *in vitro* studies. Values are expressed in micrograms of tetrazolium per mg. tissue. In chronic progressive infection there was a marked diminution in activity in the kidney with little change in other organs. With less virulent organisms there was a significant drop in the kidney with subsequent return to normal. Sensitization with dead bacilli produced no change but tuberculin

shock caused a decrease in all organs. Neither starvation nor rickettsial infection reproduced this picture. Marked alteration occurs in the kidney of infected animals. This change may be correlated with resistance and may account for some metabolic changes seen in chronic infection.

CARDIOVASCULAR EXAMINATION OF 300 PRACTICING PHYSICIANS OVER THE AGE OF FORTY. *K. Chesky, M.D., A. M. Master, M.D. and L. Pordy, M.D.* (From the Cardiographic Lab., Mount Sinai Hospital, N. Y.)

Since it has frequently been stated that heart disease is much more common among physicians than other groups of individuals, we thought it pertinent to determine the incidence and type of heart disease in 300 consecutively examined practicing physicians over the age of forty. The cardiovascular study included history, physical examination, resting 12-lead electrocardiogram, x-ray of the chest and/or cardiac fluoroscopy, resting ballistocardiogram and, when available, the flicker photometer test. If these tests were negative a single or double "2-step" Master exercise test was performed and an exercise ballistocardiogram recorded. The ballistocardiograms were recorded by the simple displacement type photoelectric cell instrument devised by Dock as modified by us. There was a high incidence of cardiovascular abnormalities (approximately 33 per cent) in this group of physicians. The commonest type of heart disease was coronary insufficiency. The majority of physicians were overweight and used tobacco excessively. The results will be discussed in detail.

ABSORPTION OF RADIOACTIVE IRON IN NORMAL, ANEMIC AND HEMOCHROMATOTIC SUBJECTS. *R. B. Chodos, M.D. and J. F. Ross, M.D.* (From the Cushing Veterans Administration Hospital, Framingham, Mass.)

The maintenance of iron equilibrium in man is conceived to be dependent upon the regulation of iron absorption since, aside from actual blood loss, 1.0 mg. or less of iron is eliminated daily from the body. The present investigation undertakes to evaluate iron absorption in normal, iron deficient and hemochromatotic subjects. Radioactive iron was administered orally and determinations made of (1) the quantity appearing in feces and hence not absorbed, (2) the quantity incorporated in hemoglobin and (3) the quantity not appearing either in hemoglobin or feces and hence presumed absorbed and deposited in body iron stores. Data on the absorption of iron by twenty-five subjects have been accumulated. Normal subjects incorporated 1 to 10 per cent into hemoglobin and 66 to 90 per cent was recovered in feces, while iron deficient subjects incorporated 40 to 62 per cent into hemoglobin and 34 to 67 per cent was recovered in feces. Hemochromatotic subjects with excess body iron stores incorporated 0.5 to 11 per cent into hemoglobin, while 84 to 98.5 per cent was recovered in feces. These data suggest that patients with established hemochromatosis may be absorbing less iron than normal subjects and that the extent of saturation of body iron stores may be a factor in the control of the absorption of iron. Our observations are in marked divergence from the current concept of iron absorption by patients with hemochromatosis.

COMPARATIVE EFFECTS OF H.P.C. (3-HYDROXY-2-PHENYLCINCHONINIC ACID) AND ASPIRIN IN ACUTE RHEUMATIC FEVER. *E. J. Clark, M.D. and H. B. Houser, M.D.* (*introduced by E. O. Hahn, M.D.*). (From the Medical Service, USAF Hospital, and Streptococcal Disease Lab., Francis E. Warren Air Force Base, Wyoming; Dept. of Preventive Medicine, Western Reserve Univ. School of Medicine, Cleveland, O.)

Preliminary reports indicate that H.P.C. (3-hydroxy-2-phenylcinchoninic acid) favorably alters the course of acute rheumatic fever. The present study was designed to compare the effects of H.P.C. and aspirin on the clinical course of acute rheumatic fever and carditis in young adults. Thirty-four patients were treated with H.P.C. and thirty-five with aspirin for six weeks; dosage was determined by body weight. Daily observations were recorded for nine weeks and thereafter at monthly intervals. H.P.C. did not relieve joint symptoms or fever as rapidly as did aspirin. During therapy aspirin exerted a more marked effect on the sedimentation rate. After cessation of treatment symptoms returned with equal frequency in each group. There was no apparent difference in the effect of these two compounds on either acute carditis or incidence of heart murmurs at nine months after treatment. It is concluded that H.P.C. is not as effective as aspirin in relieving symptoms of acute rheumatic fever. No apparent difference

exists between these two drugs as far as their ability to alter acute carditis.

STUDIES OF FRUCTOSE METABOLISM IN INSULIN RESISTANT DIABETES. *J. W. Craig, M.D.,* Max Miller, M.D., Hiram Woodward, Jr., M.D.* and W. R. Drucker, M.D.** (From the School of Medicine, Western Reserve Univ., Cleveland, O.)

Others have reported that fructose is utilized better than glucose by diabetic patients but that this advantage disappears after prolonged administration. This problem has been reinvestigated in a patient requiring 1,100 units of insulin daily. Insulin was withdrawn and 100 gm. of fructose were given intravenously each morning for nine days. Blood fructose disappearance curves, blood pyruvate and phosphorus levels, and urinary fructose excretion were similar to those found in normal subjects and were unchanged after nine days. Similar studies following nine days of oral administration also revealed no loss of fructose tolerance. Fructose was utilized better than glucose administered by either route. Blood fructose disappearance curves were not altered by insulin. For two weeks the patient received a constant diet to which 138 gm. of either fructose or glucose was added on alternate days. When the sugars were thus distributed in the diet, the twenty-four-hour urinary excretion of hexose did not demonstrate any striking advantage of fructose over glucose. Possible explanations for this apparent discrepancy will be presented. The implication of these findings with regard to the prevailing concepts of carbohydrate metabolism and the site of insulin action will be discussed.

EFFECTS OF P-(DI-N-PROPYLSULFAMYL) BENZOIC ACID (BENEMID®) ON FREE AND TOTAL SULFONAMIDE PLASMA LEVELS. *A. P. Crosley, Jr., M.D., G. M. Bayne, M.D.,* S. Carfagno, M.D.* and W. P. Boger, M.D.* (From the Norristown State Hospital, Norristown, Pa.)

Enhancement of plasma-penicillin levels by benemid® is of therapeutic advantage in a number of clinical states. The likelihood that sulfonamides may be employed concomitantly with benemid and penicillin, and the structural similarity between sulfonamides and other compounds whose renal transport is affected by benemid suggested exploring the effects of this agent upon sulfonamide plasma concentrations following oral and intravenous administration of triple sulfonamide combinations. Twelve individuals were used as their own controls in a cross-over type of experiment. It seemed advantageous in a preliminary investigation of this kind, designed to test an effect upon the sulfonamide group of compounds, to select a triple mixture rather than a single sulfonamide. Such triple sulfonamide mixtures currently enjoy a wide use based upon their relative freedom from urinary complications. There is little in the literature on the plasma concentrations attained with such combinations. Following intravenous administration of a single dose of the sulfonamides there was an increase in the total sulfonamide levels during benemid administration, amounting to a mean difference of 1.44 mg. per cent. With an orally administered mixture benemid caused an increase in both free (mean difference—2.18 mg. per cent) and total sulfonamide (mean difference—4.56 mg. per cent) plasma levels. These differences are statistically significant ($p < .001$). The benemid effect was maximal on the third day and remained constant thereafter. The clinical significance of these data will be discussed.

EXPERIENCE WITH A STANDARDIZED BROMSULFALEIN PLASMA CLEARANCE METHOD AS A SENSITIVE TEST OF LIVER FUNCTION. *J. W. Culbertson, M.D., T. L. Welton, M.D.,* K. H. Kinard, M.D.* and J. G. Easton, M.D.** (From the Cardiovascular Lab., State Univ. Iowa College of Medicine, Iowa City, Ia.)

Plasma clearance rate of bromsulfalein represents the state of both liver circulation and hepatocellular metabolism and is influenced by changes in either. Thus it measures actual function at the time of testing (rather than reserve functional capacity) and promptly reflects acute changes in hepatocellular excretory activity during experimental observation. Standardization is accomplished by infusing intravenous BSP constantly at 2.5 mg./min./sq.M., allowing twenty minutes for equilibration and pilot blood sampling, and drawing venous (or arterial) blood samples at thirty, forty, fifty and sixty minutes. Calculations are made from plasma concentration, its rate of change and the infusion rate. C_{BSP} is expressed in ml./minute. Thirty-eight hospitalized patients were studied. Nineteen men (ages 17–75, av. 36) ranged from 163 to 955 (average 610). Nineteen women (ages 16–57, av. 34) ranged from 160 to 1,054 (average 489). Distribution was rather

even in both groups. Known and suspected cases of liver disease fell neatly in the lower ranges. Moreover, unsuspected hepatic dysfunction was found in some patients. Functional improvement under therapy was demonstrated quantitatively. Acute spontaneous increases and decreases in clearance rates were observed, and acute reductions were induced experimentally by both physiologic and pharmacologic means. The method is sensitive and versatile.

STUDIES ON THE PHYSIOLOGY OF AWARENESS: DIFFERENTIAL INFLUENCE OF OLFACTORY STIMULATION AND EFFECT ON ARTERIAL OXYGEN. *J. W. L. Doust, M.D. and R. A. Schneider, M.D.* (From the Institute of Psychiatry, Maudsley Hospital, London, England.)

Twenty-five healthy control subjects and forty-three patients with a variety of psychiatric disorders were investigated by spectroscopic oximetry to determine their resting arterial oxygen saturation levels and the possible influence of a number of different odors on such levels. Twelve substances ranging from coffee and perfume to asafoetida and acetic acid and contained in indifferently labeled bottles were separately presented to the subject and he was requested to sniff strongly at them and then to state whether the odor was regarded as "pleasant" or "unpleasant." Oximetric readings were taken during the time the subject was smelling each bottle. Unequivocal decline in oximetric readings took place in both groups of subjects on presentation of all the olfactory stimuli. The extent of anoxemia appeared to depend not so much on the actual substance exposed as on the subject's individual reaction to it in terms of his hedonic feeling-state. A smell termed pleasant by one subject was not necessarily considered so by the next and pleasant odors induced far less anoxemia than did those rated as unpleasant, percentage oxygen saturation falling typically, e.g., from 94 to 88 as a pleasant odor was exchanged for an unpleasant one in a healthy subject whose resting level was 98 per cent oxygen.

THE KEY TO THE CIRCULATION IN CONGENITAL HEART DISEASE. *J. W. Dow, M.D.* (From the Lovelace Clinic, Albuquerque, N. Mex.)

Seventy-five patients with congenital cardiovascular anomalies were studied by venous catheterization. Flows through periphery and lung were calculated according to the Fick principle. Orifice sizes were estimated by the methods of Gorlin and Gorlin, and resistances offered by the whole secondary circuit, by the orifice, by the distal pulmonary vasculature and by the post-pulmonary vasculature were derived from the relation: (resistance equals pressure gradients/flow through circuit). Peripheral blood flow and arterial perfusion pressure were maintained within normal limits. Pulmonary arterial pressures ranged from very low to figures approximating the systemic pressures. Similarly, flow through the lung varied from a fraction of the systemic to many times the volume. Secondary circuits flows and pressures were largely controlled by the location and magnitude of resistance. When total resistance to flow through the secondary circuit was high, flow was small, and conversely large flows were found with low resistance. High resistance at a small orifice tended to create a wide orifice gradient and to permit normal or low pulmonary arterial pressure. The low resistances offered by large orifices tended to make large gradients impossible at any flow, leading to approximation of pressures in pulmonary and peripheral circuits. High resistance distally favored high pulmonary arterial pressure by creating a big vascular gradient and by reducing the gradient due to flow across an orifice of any given size. Low distal resistance favored low pulmonary arterial pressure by increasing flow and gradient across a fixed orifice. The jealous guarding of systemic blood flow serves as a reminder that tissue perfusion is the primary purpose of the heart and circulation, to which all other considerations must be subordinated. Maintenance of a suitable pressure head in the aortic reservoir is the immediate prerequisite to differential tissue perfusion. The systemic ventricle must always pump enough blood against the prevailing total resistance to create a system of gradients the sum of which is equal to the necessary pressure head. Conditions in the secondary pulmonary circuit must therefore be keyed to systemic arterial pressure. Flow through the lung will be whatever volume will traverse that circuit at the particular systemic pressure required. Pulmonary circuit pressures will depend upon the site and magnitude of resistances. For any given set of circumstances dynamic conditions within the divisions of the pulmonary circuit are easily predictable.

STUDY OF REFLEX VENOMOTOR REACTIONS IN MAN. *J. J. Duggan, M.D., V. L. Love, M.D.* and R. H. Lyons, M.D.* (From the State Univ. of New York College of Medicine, Syracuse, N. Y.)

Under usual conditions the larger part of the total blood volume lies within veins. Many of these veins are provided with smooth muscle and autonomic innervation. The potential significance of a variable venomotor tone in circulatory homeostasis has been noted by many observers, but specifically venomotor reactions have been difficult to demonstrate in the human. By the use of simple clamps we have been able temporarily to isolate a segment of forearm vein from the circulation so that change in pressure within the segment measures change in venous tone. Reflex venoconstriction was elicited by inspiration against resistance, immersion of the opposite hand in ice water, rebreathing of a 5 per cent CO_2 mixture and voluntary hyperventilation. The effect of apprehension was observed on occasion. Reflex venoconstriction could be blocked by procaine infiltration around the vein proximal to the segment being studied, by the administration of tetraethylammonia and sometimes by stellate block. These results indicate that efferent venomotor fibers traverse autonomic ganglia and follow peripheral sympathetic pathways. The magnitude of the response obtained, which sometimes reached a pressure rise of 50 mm. Hg in relatively poorly muscled veins, supports the concept that neurogenic venomotor reactions may be quantitatively significant in circulatory adjustments.

RENAL VASODILATOR EFFECTS OF 1-HYDRAZINOPHTHALAZINE IN HYPERTENSIVE PATIENTS. *H. P. Dustan, M.D., A. C. Corcoran, M.D., R. D. Taylor, M.D. and I. H. Page, M.D.* (From the Cleveland Clinic Foundation, and the Frank E. Bunts Educational Institute, Cleveland, O.)

Incidence, degree and locale of renal vasodilation following an intravenous test dose of 1-hydrazinophthalazine were examined in fifty patients and evaluated by Gomez' formulas. Responses were inconstant and occasionally vasoconstrictor. However, the following mean percentile decreases of total resistance, R, were found on classification of the patients by groups: (1). −31 (essential hypertension, 19 cases); (2a). −28 (malignant hypertension, relatively stationary, 10); (2b). −6 (malignant hypertension, rapidly advancing, 9); (3). −16 (renal hypertension, 10); (4). −33, (post-toxemic hypertension, 2). Changes in R_A, R_E and R_V paralleled R, except in sub-group 2b. Responses of arterial pressure were relatively uniform (−7 to −11 per cent) among the groups. Thirteen patients whose responses to subsequent prolonged oral treatment were favorable showed a mean test R of −33 per cent while thirteen whose responses were not favorable showed a mean test R of −17 per cent. The data suggest that the renal hemodynamic response to an intravenous test dose of 1-hydrazinophthalazine may, (1) aid in characterizing hypertension of renal origin and (2) segregate patients who do *not* respond favorably to oral medication. In contrast, the immediate depressor response has neither diagnostic nor prognostic value.

METABOLISM OF RADIOACTIVE ZINC-65 IN PATIENTS WITH MALIGNANT DISEASE. *F. G. Ebaugh, M.D. and J. F. Ross, M.D.* (From the Evans Memorial, Massachusetts Memorial Hospitals, and the Dept. of Medicine, Boston Univ., Boston, Mass.)

Differences in the zinc content between normal and neoplastic tissues and between leukemic and non-leukemic leukocytes have been demonstrated by others. The purpose of this study was to explore the dynamics of zinc metabolism in patients with leukemia and other malignant disease. Radioactive zinc-65 ammonium citrate was administered to the patient intravenously. Fifty per cent of the injected zinc was cleared from the plasma in fifteen minutes; 90 per cent in thirty minutes. The maximum uptake of zinc-65 by the erythrocytes occurred on the ninth day. For the next ninety days the erythrocyte zinc-65 fell linearly with time and approached zero on the 90th to 120th day. The maximum leukocyte uptake of zinc-65 was two to four times greater than that of the erythrocytes. Analysis of the leukocyte uptake curves revealed a life span of leukemic granulocytes of from fifteen to forty hours. The life span of leukemic lymphocytes was considerably longer. Non-leukemic leukocytes took up three times more zinc-65 than did leukemic leukocytes. Data have also been obtained on the biologic half life, excretion, distribution in postmortem tissues and anatomic location of zinc-65 in the cell.

STUDIES OF THE SITE AND CONTROL OF ERYTHROPOIESIS. *P. J. Elmlinger, M.D.,* R. L. Huff, M.D.,* D. C. Van Dyke, M.D.* and J. H. Lawrence, M.D.* (From the Donner Laboratory and the Institute for Experimental Biology, Univ. of California, Berkeley, Calif.)

Iron turnover studies on more than seventy-five patients and seven normal subjects by serial blood "sampling" and *in vivo* "counting" after intravenous injection of Fe^{59} globulin indicate that such studies are a very promising diagnostic tool. Some problems easily solved by this unique test are: (1) Splenomegaly associated with extramedullary erythropoiesis is easily differentiated from that associated with splenic destruction of essentially normal red cells or removal of defective red cells. (2) Refractory anemias with erythroid hyperplasia (intra- or extramedullary) are easily distinguished from refractory anemias with erythroid hypoplasia. (3) In certain carcinoma cases, as also in rheumatoid arthritis, excessive iron turnover through abnormal accessory non-erythrogenic pathways may be differentiated from excessive turnover via red cells. Administration of oxygen decreases the iron turnover in plasma and red cells in secondary polycythemia but not in polycythemia vera. The long known fact that transfusion-induced plethora inhibits marrow erythrogenesis has been confirmed in rats by the depression of the red cell iron turnover by transfusion to greater than normal red cell volume. A number of separate yet interrelated projects on the control of erythropoiesis are under way. Of particular interest is the work in isolation of a substance possibly related to the humoral mediation of the erythropoietic stimulus of anoxia.

EFFECT OF ACUTE OCCLUSION OF AN ARTERIOVENOUS FISTULA ON CARDIAC DYNAMICS, RENAL FUNCTION AND ELECTROLYTE EXCRETION. *F. H. Epstein, M.D., Robert S. Post, M.D.,* M. E. McDowell, M.D.,* O. W. Shadle, M.D.* and T. B. Ferguson, M.D.** (From the Army Medical Service Graduate School, Walter Reed Medical Center, Washington, D. C.)

A unique opportunity to study the responses of the heart and the kidneys to sudden sustained alterations in peripheral resistance and in the distribution of blood in the vascular tree presents itself in the patient with a traumatic peripheral arteriovenous fistula. Cardiac output was measured in six such subjects by instantaneous injection of dye through a cardiac catheter while intracardiac and peripheral arterial pressures were recorded. Following control periods, temporary occlusion of the fistula resulted in an increase in arterial blood pressure and a fall in pulse rate in all patients. Mean pressures in the right atrium and pulmonary artery remained unchanged or decreased slightly. Cardiac output and stroke volume fell in four patients in whom "resting" values were elevated. Renal excretion of sodium increased markedly in fifteen patients during manual compression of the fistula and decreased following release. Renal venous pressure, renal blood flow and glomerular filtration rate did not change significantly during compression. After repair of the fistula compression over the operative site or the opposite artery was without effect on sodium excretion. These findings are consistent with the hypothesis that renal excretion of salt may be conditioned by the degree of distention of some portion of the arterial tree.

EFFECT OF LEFT SPLANCHNIC NERVE DIVISION ON THE RENAL EFFECTS OF ACUTE VENOUS CONGESTION. *S. J. Farber, M.D., D. P. Earle, M.D. and C. F. Baxter, M.D.** (From the Dept. of Medicine, New York Univ. College of Medicine, N. Y.)

Acute venous congestion in anesthetized dogs produced by inflating a balloon in the superior or inferior vena cava decreases salt and water excretion. The present study deals with the effect of division of the greater splanchnic nerve on this response. In five dogs the left splanchnic nerve was cut and urine collected from exteriorized ureters. Venous congestion of 150 mm. of water was produced for thirty minutes in the inferior vena cava above the renal veins or in the superior vena cava. The right kidney decreased its excretion of salt and water to the extent previously observed. The decrease in excretion of salt by the left kidney was not great. During venous congestion in two animals salt excretion on the left was higher than the control values. The average of all ratios obtained by dividing sodium excretion during congestion by control sodium excretion in four animals was 0.35 on the right and 0.98 on the left. The fifth animal had very low control sodium excretions and congestion still produced a greater decrease on the right. These low values did not justify the use of these ratios in

the computed averages. Renal hemodynamics showed variable changes and usually were not directly related to changes in water and salt excretion. Venous congestion in an operated animal whose left splanchnic was not divided produced equal reductions in salt and water excretion bilaterally. It is concluded that left splanchnic nerve division alters the response of the kidney to acute venous congestion.

WIDESPREAD OCCURRENCE OF TOXOPLASMA ANTIBODIES IN MAN AND VARIOUS ANIMALS. *H. A. Feldman, M.D.* (From the Dept. of Medicine, State Univ., New York Medical Center at Syracuse, Syracuse, N. Y.)

The recent detection of two adults with fatal acquired toxoplasmosis, and the reports of a number of cases of a syndrome characterized by fever, lymphadenopathy, carditis, etc., have served to stimulate interest in the disease potentialities of toxoplasma. Since the source of human infections is unknown and only limited information on the distribution of antibodies in humans is available, the antibody status of human beings and animals was investigated by means of the skin and dye tests. Information so obtained indicates that antibodies for toxoplasma are commonly encountered in both of these groups throughout a broad geographic area. Samples of the "normal" populations of Cincinnati and Syracuse, New York, were surveyed with the skin test; although the patterns were somewhat different, no positive reactors were found under the age of four years. From that point on there was a constant increase in positive reactors until, by middle age, about half the population samples reacted to the antigen. Serologic tests have been performed with specimens from a number of American cities with somewhat similar results. Among the various animals studied, dogs, cats and guinea pigs appear commonly to be infected. Although the congenital disease has been demonstrated in many parts of the world the diagnosis, by serologic methods, of acquired toxoplasmosis should be made with caution.

EFFECTS OF ACUTE ELEVATION OF SERUM POTASSIUM AND SODIUM CONCENTRATIONS ON THE CANINE ELECTROCARDIOGRAM. *F. W. Fitzhugh, Jr., M.D. and J. T. Doyle, M.D. (introduced by A. J. Merrill, M.D.).* (From the Dept. of Medicine, Emory Univ. School of Medicine, Atlanta, Ga.)

The electrocardiograms of patients with elevated serum potassium concentrations fail to reveal a close correlation between the severity of the electrical changes of hyperkalemia and either serum or intracellular potassium concentrations, as determined by muscle biopsy. The following studies have been made in an attempt to elucidate the electrolyte factors causing this lack of correlation. Intravenous infusions of isotonic potassium chloride solution were given to dogs. Classical electrocardiographic changes of hyperkalemia appeared and fatal cardiac arrest regularly occurred at serum potassium concentrations of 10 to 12 mEq./L. Serum sodium concentration decreased as potassium rose. Tissue electrolyte determinations failed to reveal appreciable changes in intracellular sodium and potassium concentrations during such acute experiments. When potassium chloride and hypertonic sodium chloride were infused simultaneously, the electrocardiogram was little affected at serum potassium levels of 15 mEq./L. or greater. High concentrations of serum sodium alone produced no cardiotoxic effect. It is concluded that the electrocardiographic changes of hyperkalemia may occur irrespective of changes in intracellular sodium and potassium concentrations. Furthermore, the elevation of serum sodium concentration to supernormal levels appears to protect against the electrocardiographic changes of hyperkalemia.

NEOTETRAZOLIUM AS A HISTOCHEMICAL INDEX OF CELL METABOLISM IN THE OVARY. *A. G. Foraker, M.D. and S. W. Denham, M.D.** (From the Emory Univ. School of Medicine, and Grady Memorial Hospital, Atlanta, Ga.)

Tetrazolium salts as indicators of dehydrogenase activity are new additions to the histochemical armamentarium. An insoluble formazan is said to be formed at sites of metabolic processes. To test the pattern of formazan deposition in relation to cell metabolism, ovaries from rabbits undergoing Friedman tests were processed in neotetrazolium. Ovaries from all rabbits revealed diffuse blue-black granular deposition through the stroma, with heavier deposition in follicular cells of the numerous ova. Numerous cystic follicles were found in ovaries of rabbits injected with urine from non-pregnant women. The granulosa cell layer of these generally had a deposition of small formazan granules, usually somewhat more concentrated than in the adjacent stroma. In ovaries of

rabbits injected with urine from pregnant women the cell layers of the corpora hemorrhagica and corpora lutea usually contained much heavier formazan deposits with larger granules than seen elsewhere. Cell layers adjacent to some of the largest hemorrhages occasionally had little or no formazan deposition. This may result from (1) chemical interference by the blood in the hemorrhagic follicle and (2) diminution of cellular metabolism of adjacent tissue once massive hemorrhage has occurred. The pattern and degree of formazan deposition corresponded to anticipated areas of intense cellular metabolism in the ovary.

SOME CONDITIONS RESULTING IN LOCALIZED OR SYSTEMIC LOSS OF TISSUE POTASSIUM. *C. L. Fox, Jr., M.D., J. M. Winfield, M.D.* and Sigmund Kasker, M.D.* (From the Dept. of Surgery and Pediatrics, N. Y. Medical College, Flower and Fifth Avenue Hospitals, New York, N. Y.)

The importance of potassium (K) in cellular metabolism emphasizes the value of information regarding factors which regulate its cellular concentration. The following studies indicate some of the circumstances which may be accompanied by either localized or systemic losses of tissue K. By serial replacement of three-fourths of the blood of dogs with electrolyte solution, hypopotassemia, anemia and hypoproteinemia were produced in three hours. Hyperpotassuria followed and approximately 20 per cent of total body K was excreted in the urine. Equivalent infusions without hemorrhage had no such effects. Tissue K replenishment occurred gradually as K almost disappeared from the urine. Since dog erythrocytes contain little K, their regeneration was not a factor. In contrast, localized tissue anoxia produced by tourniquets resulted in loss of 60 per cent of injured muscle K with slight changes in contralateral, uninjured muscles. Similarly the localized injection of alpha toxin (lecithinase) of Cl. welchi induced practically identical loss of muscle K. After major surgical operations the traumatized rectus muscles in the operative zone lost up to 55 per cent of K compared to preoperative values. Scant change occurred in the non-traumatized thigh muscles. In one of these patients systemic losses of tissue K were found at autopsy after ten days of hyperpotassuria. Systemic loss of tissue K occurred in a patient with the nephrotic syndrome during two repeated courses of ACTH not followed by diuresis; a third course marked by K retention was followed by diuresis with 50 per cent reduction in body weight. Autopsy tissues of other patients with the nephrotic syndrome revealed depletion of K of skeletal muscle but not of liver or kidney. Correlation of the diverse conditions associated with localized or systemic loss of K may elucidate the underlying mechanisms involved.

POSTOPERATIVE CHANGES IN LIVER FUNCTION. *A. B. French, M.D., C. M. Jones, M.D.,* R. R. Linton, M.D.,* D. S. Ellis, M.D.* and H. K. Beecher, M.D.** (From the Massachusetts General Hospital, and the Depts. of Medicine, Surgery and Anesthesia, Harvard Medical School, Boston, Mass.)

Clinical observations and changes in liver function tests following sixteen gastrectomies, twenty-two cholecystectomies and thirty-seven shunt operations for the relief of portal hypertension are described. A distinct pattern of liver function test changes was noted, which varied with the type of operation and degree of preoperative liver damage. Following gastrectomy fourteen patients showed bromsulfalein retention which often reached a peak as high as 28 per cent several days after operation and usually returned to normal by the tenth postoperative day. After cholecystectomy bromsulfalein retention was greater and more prolonged with peaks as high as 64 per cent retention. With these operations abnormalities in other liver function tests (including serum bilirubin, urine urobilinogen, plasma prothrombin time and serum alkaline phosphatase) were sometimes present but were not pronounced. After shunt operations for the relief of portal hypertension, bromsulfalein retention, rises in serum bilirubin, urine urobilinogen, and prothrombin time were greater and more prolonged than the changes which followed operation in patients with normal livers. The changes varied with the degree of preoperative liver dysfunction. A hitherto undescribed finding was an early postoperative fall in serum alkaline phosphatase followed by a prolonged rise which in one case reached 122 Bodansky units. Six deaths from a larger series of shunt operations are discussed.

CIRCULATORY CONSEQUENCES OF PNEUMOPERITONEUM IN PULMONARY EMPHYSEMA. *R. H. Furman, M.D., T. M. Blake, M.D. and M. T.*

*Stahlman, M.D.** (From the Vanderbilt Univ. School of Medicine, Nashville, Tenn.)

An increasing experience with pneumoperitoneum has suggested that benefit may accrue to the patient which is difficult to assess by common pulmonary function tests. Utilizing cardiac catheterization, seven severely emphysematous subjects with low immobile diagrams were studied at rest and after exercise. Resting output values were low and showed variable but slight change after pneumoperitoneum. Exercise before pneumoperitoneum produced a fall in cardiac output in five, no change in one and a rise in another. No fall was noted following exercise after treatment. Two subjects whose outputs fell after exercise before pneumoperitoneum showed no change following exercise after treatment; output rose in five. Exercise in every instance evoked maximal ventilatory responses. The post-pneumoperitoneum improvement in the cardiodynamic response to exercise was associated with an increased oxygen consumption and extraction and smaller A-V oxygen difference than that noted following exercise before treatment. Increased intrapleural-intraperitoneal pressure differentials and probably improved intrapulmonary gas mixing appear to be the responsible mechanisms. The same mechanisms may obtain in the familiar squatting posture seen after exercise in patients with tetralogy of Fallot.

URINARY EXCRETION OF AMINO ACIDS IN PATIENTS WITH CIRRHOSIS OF THE LIVER AND IN NORMAL ADULTS. *G. J. Gabuzda, M.D., R. D. Eckhardt, M.D. and C. S. Davidson, M.D.* (From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Dept. of Medicine, Harvard Medical School, Boston, Mass.)

The urinary excretions of the ten "essential" amino acids were determined microbiologically in twenty patients with hepatic cirrhosis and in fourteen normal individuals. The effect of increases in protein intake and of clinical improvement upon amino acid excretion was determined in metabolically controlled studies. The average daily excretions of arginine, leucine, methionine, phenylalanine, threonine, tryptophane and valine were slightly higher in the twenty patients than in the controls; and those for histidine, isoleucine and lysine were slightly lower. The pattern of the amino acids excreted by the patients was similar to the normal. Increased methionine and tryptophane and decreased isoleucine excretions were the most marked alterations observed in the patients. Urinary wastage of amino acids did not result from large increases in dietary protein intake (four patients). Progressive decreases in the excretion of all the amino acids studied accompanied improvement in liver disease in three patients followed for two to five weeks. *Conclusions:* Compared with calculated intakes the increased amino acid excretions observed were not nutritionally significant. The increased urinary excretion of amino acids by patients with hepatic cirrhosis depends more upon the activity of the disease than upon the dietary protein intake.

RECOVERY OF BROMSULFALEIN FOLLOWING INTRAVENOUS AND ORAL ADMINISTRATION. *B. Giges, M.D., W. C. Morse, M.D., W. S. Sharon, M.D. and J. Wynn, M.D. (introduced by V. M. Sborov).* (From the Dept. of Hepatic and Metabolic Diseases, Walter Reed Army Medical Center, Washington, D. C.)

In the normal human subject about 55 to 65 per cent of intravenously injected bromsulfalein (BSP) can be recovered by analysis of the urine and feces. Since virtually all of the BSP appears in the bile, the possibility that the dye was altered in the intestinal tract was considered. BSP was, therefore, given orally to evaluate this possibility. Less than 30 per cent of the amount given was recovered in the feces and none in the urine. To determine which factors were important in destroying the dye, BSP was incubated with stool suspensions and with sterile stool filtrates. The results indicate that the normal intestinal flora is capable of altering the BSP molecule in such a way as to prevent development of its characteristic color upon addition of alkali. No effect was produced in the absence of bacteria. Observations made in patients with liver disease indicated that BSP was destroyed at the same rate as in normals.

HEPATIC BLOOD FLOW MEASUREMENT IN THE DOG: EVALUATION OF THE BROMSULFALEIN EXTRACTION METHOD. *B. Giges, M.D., P. E. Teschan, M.D. and W. S. Sharon, M.D. (introduced by V. M. Sborov).* (From the Dept. of Hepatic and Metabolic Diseases, Walter Reed Army Medical Center, Washington, D. C.)

Hepatic blood flow was estimated in thirty-five normal dogs under nembutal anesthesia by the bromsulfalein extraction method using hepatic vein catheterization. To obtain the optimal plasma BSP concentration of 1 to 2 mg. per cent, a priming dose of 2 mg. per kg. of body weight was given and a sustaining infusion was delivered at the rate of 0.07 to 0.1 mg. per kg. per minute. Urinary loss of dye is insignificant when the plasma concentration remains below 2 mg. per cent. The average value for estimated hepatic blood flow in thirty-five dogs was 35 ml. per kg. per minute, with a range of variation from 20 to 50 ml. per kg. per minute. In six animals duplicate experiments were performed and values for the estimated hepatic blood flow were in close agreement. The error of the method was 20 per cent as calculated both from the duplicate experiments and the variation in the course of any single experiment. Using this method the effects of adrenalin, histamine, decholin and ACTH in varying doses on the estimated hepatic blood flow have been studied in normal and splenectomized animals.

DISTRIBUTION OF PLASMA PROTEINS IN THE TISSUES OF INFANTS AND CHILDREN. *D. Gitlin, M.D., B. H. Landing, M.D. and A. Whipple, M.D.* (*introduced by C. A. Janeway*). (From the Harvard Medical School, and Children's Medical Center, Boston, Mass.)

The distribution of plasma albumin, γ-globulin, β-lipoprotein, β_1-metal combining globulin and fibrinogen has been studied in the tissues of infants and children. Using labelled antibodies specific for the individual plasma protein, the proteins were detected in Linderström-Lang sections of tissues obtained at biopsy or autopsy. In this study were three patients with erythroblastosis fetalis, three patients with congenital heart disease, one with bronchiolitis and two with brain tumors. The tissues studied were heart, lung, spleen, esophagus, stomach, small intestine, colon, pancreas, liver, kidney, adrenal, bladder, skeletal muscle, skin, lymph node, aorta, tongue, larynx, thyroid, thymus, cartilage, bone marrow and brain. Small amounts of the plasma proteins studied were found in the cells of many organs but the greatest extravascular quantities were found in connective tissue. The results appear to indicate that human tissues do not have significant reserves of preformed plasma protein, any store of such protein being in the interstitial tissue. In some instances differences in the tissue distribution of the individual proteins were demonstrated.

The significance of the small cellular concentrations of plasma proteins in relation to their formation and migration to and from the plasma is considered.

EFFECTS OF INORGANIC IODIDE ION ON THE RATE OF RELEASE OF HORMONE FROM THE THYROID IN THYROTOXIC HUMAN SUBJECTS. *R. E. Goldsmith, M.D. and M. A. Blankenhorn, M.D.** (From the Cincinnati General Hospital, Cincinnati, O.)

The iodine-induced remission in thyrotoxicosis has been well documented since the pioneer work of Plummer. Explanations of the phenomenon usually offered are (1) the iodine interferes with the release to the periphery of thyroid hormone and (2) the iodine interferes with the usual action of thyrotropin. Four patients with diffuse goiter and thyrotoxicosis have been studied by the following method: I^{131} was introduced into the thyroid hormone pool; a blocking agent, 1-methyl-2-mercatoimidazole, was then given to prevent further synthesis of hormone. The hormone decay rate of the block thyroid was established by daily *in vivo* and urinary measurements of labelled iodine; I^{127} was added to this regimen in three patients and any change in the hormone decay rate was noted. One control patient was studied on the blocking agent alone. The control patient maintained a constant hormone decay rate throughout the study. The other three patients showed a significant decrease in hormone decay rate when I^{127} was added as compared to that noted on the blocking agent alone. The implications of these data will be discussed.

EFFECTS OF HYPOXIA ON THE PULMONARY CIRCULATION OF THE DOG. *R. Gorlin, M.D.* (From the Medical Clinic, Peter Bent Brigham Hospital, and the Dept. of Medicine, Harvard Medical School, Boston, Mass.)

Many current investigations have demonstrated varying pulmonary vascular reactions to hypoxia. Sixteen dogs previously anesthetized with morphine-chloralose-urethane were subjected to breathing mixtures varying in oxygen from 2.5 to 10 per cent. Cardiac output was measured by the Fick method and pulmonary arterial (PA) and left arterial (LA) pressures

recorded. Pulmonary vascular resistance (PVR) was calculated from the Poisseuille equation. When arterial oxygen saturation was below 55 per cent, the PA-LA pressure gradient remained unchanged or increased slightly, cardiac output uniformly rose and PVR fell. This response occurred regardless of duration of hypoxia. When arterial oxygen saturation was above 55 per cent, the PA-LA pressure gradient increased, cardiac output changed little and PVR increased. PVR increased progressively the longer the duration of hypoxia was above 55 per cent. The level of cardiac output seemed related to arterial oxygen saturation. Mild hypoxia caused no increase in cardiac output. Pulmonary vasoconstriction, however, did occur, probably due to the local effects of hypoxia on the pulmonary vessels. Severe hypoxia altered bodily homeostasis, leading to a rise in cardiac output and dilatation of pulmonary vessels or at least an inhibition of the local vasoconstriction effects of hypoxia.

SERUM MUCOPROTEIN CONTENT IN THE DIAGNOSIS OF JAUNDICE AND/OR HEPATOMEGALY. *E. M. Greenspan, M.D.* (From the National Cancer Institute, Bethesda, Md., and the Mount Sinai Hospital, New York, N. Y.)

In an extension of previous studies the content of serum mucoprotein (M) and alpha-1-globulin was estimated in eighty-nine normal adult subjects. The normal limits of M, estimated as biuret peptide, varied from 40 to 70 mg. per cent in females (mean & S.D. = 54.3 ± 7.7) and 48 to 75 mg. per cent in males (60.3 ± 7.4). Determinations were performed in 171 patients with jaundice or hepatomegaly classified as follows: (I) Infectious hepatitis, homologous serum hepatitis or portal cirrhosis; (II) obstructive inflammatory or neoplastic disease of the biliary tract (acute or chronic cholecystitis, common duct stone, cholangitis, biliary cirrhosis and biliary or pancreatic carcinoma); (III) hepatomegaly due to hepatic metastases. In Group I approximately 80 per cent of patients with portal cirrhosis and 90 per cent with infectious or homologous serum hepatitis showed a low M level on admission to the hospital. In Group II the M level was normal or elevated in all patients observed. The M level was elevated in more than 90 per cent of patients in Group III and normal in the remainder. The normal M level appears to represent an equilibrium between an intrahepatic factor (liver function) and such extrahepatic factors as cellular proliferation, necrosis and inflammation. An M determination may be useful in the diagnosis of diffuse parenchymatous liver disease as well as in the medical or surgical management of patients with hepatomegaly and jaundice.

HEXAMETHONIUM SALTS ALONE OR WITH 1-HYDROZALINE OR REGITINE FOR PATIENTS WITH HYPERTENSION. *K. S. Grimson, M.D.* (From the Dept. of Surgery, Duke Univ. School of Medicine, Durham, N. C.)

Tests in animals and man reveal that hexamethonium bromide, chloride, bitartrate and citrate administered parenterally produce hypotension with minimum tachycardia, interrupted vasomotor reflexes and delay transit time of barium, actions resembling those of the ganglionic blocking agent, etamon.® Single oral doses of 1 gm. of the bromide, chloride or bitartrate produce minimal effects. However, during the first several days evidence of effectiveness developed in each of sixty patients now continuing treatment, 2 to 6 gm. daily, as long as seventeen months. Most patients have relief of symptoms, some have moderate and a few have marked reduction of blood pressure. 1-Hydrozaline, apresoline,® initially tested and given to patients in 1948, occasionally reduced blood pressure when 100 mg. were given intravenously or as much as 250 mg. orally. Continuous oral treatment was discontinued because of little reduction of pressure and occurrence of side effects. Regitine,® an imidazoline derivative, was tested in 1949 using 60 or 120 mg. doses orally. It produced more reduction of pressure but continuing treatment was discontinued because of tachycardia. Apresoline or regitine has now been given to those of the sixty patients taking hexamethonium daily but whose blood pressure has not been satisfactorily reduced. Some additional reduction of blood pressure occurs. Tachycardia is less frequently troublesome. Of seven of these patients given intravenous injections of 50 mg. of regitine slight increase of pulse rate occurred in five and typical marked increase in only two.

A STUDY OF MECHANISMS IN THE "HYPERSPLENIC SYNDROME." *V. Groisser, M.D. and W. Ruberman, M.D.* (*introduced by J. Watson*) (From the State Univ. of New York at New York City, College of Medicine, Brooklyn, N. Y.)

The purpose of the present investigation was to evaluate two of the mechanisms believed to be involved in the pancytopenia associated with the "hypersplenic syndrome."

Twenty-five patients with varied hematologic disorders, including six patients with hypersplenism, were given adrenalin. Five of the patients with hypersplenism were splenectomized. There was no significant quantitative or qualitative difference in the reaction observed between the patients with hypersplenism and normal subjects. No significant change was observed in hypersplenism patients following splenectomy. Patients with refractory anemia associated with a hypoplastic or aplastic bone marrow showed a leukocyte response exceeding that observed among normals. Four patients with Cooley's anemia also showed a similarly high response in their leukocyte count. There was a uniform slight increase in hemoglobin but no change in the platelet response to adrenalin.

Plasma obtained from seven patients with thrombocytopenia, five secondary to hypersplenism and two secondary to aplastic anemia, was infused into normal recipients. In no case was there any suppression of platelets. These results differ from those reported in cases of primary idiopathic thrombocytopenic purpura in which a plasma platelet factor has been demonstrated.

It would appear that the adrenalin test does not give evidence for any excessive sequestration of blood elements by the spleen in hypersplenism; and that there is no plasma platelet reducing factor present in secondary thrombocytopenic states.

ACTION OF TESTOSTERONE AND CORTISONE ON INCORPORATION OF CARBOXYL-LABELED GLYCINE INTO PROTEIN BY HUMAN LIVER SLICES. *C. M. Grossman, M.D.,* J. A. Hauschildt, M.D. and J. D. Case, M.D.* (From the Dept. of Biochemistry and Medicine, Univ. of Oregon Medical School, Portland, Ore.)

Since testosterone is known to be a nitrogen anabolic hormone and cortisone has been reported to be protein catabolic, it was anticipated that the incorporation of labeled glycine by human liver slices would be increased in the presence of the former and decreased by the latter. Pieces of liver obtained at surgery were sliced and 100 mg. wet weight of tissue were incubated with 0.33 microcuries of carboxyl-labeled glycine. Proteins were precipitated, lipid extracted and radioactivity measured. The glycine incorporated is expressed in terms of counts per minute per milligram dry protein. A significant depression of incorporation was found when testosterone was added to the incubation medium. The degree of depression paralleled the amount of testosterone present, as little as 0.01 mg. being sufficient to cause a definite effect. Greater inhibition of synthesis is caused by amounts of testosterone up to 0.3 mg. Cortisone was found to cause a similar but less pronounced depression with 0.3 mg. per 100 mg. of liver. Further work is in progress to determine if the inhibition observed is a nonspecific steroid effect. Liver has been shown by Samuels and co-workers to destroy testosterone, utilizing oxidative enzyme systems. Since the incorporation of glycine into protein is a reaction also mediated by an oxidative enzyme system, it is possible that incorporation is inhibited so long as a steroid is present because of the preferential utilization of available oxygen and adenosine triphosphate for steroid metabolism. This possibility is being investigated.

CEREBRAL BLOOD FLOW, VASCULAR RESISTANCE, OXYGEN UPTAKE AND OXYGEN TENSION IN PATIENTS WITH ESSENTIAL HYPERTENSION BEFORE AND AFTER INTRAMUSCULAR 1-HYDRAZINOPHTHALAZINE (APRESOLINE). *J. H. Hafkenschiel, M.D., C. K. Friedland, M.D.,* J. Yobaggy, M.D.* and W. A. Jeffers, M.D.** (From the Robinette Foundation, Medical Clinic, Hospital of the Univ. of Pennsylvania, and the Dept. Pharmacology, School of Medicine, Univ. of Pennsylvania, Phila., Pa.)

Eight measurements of cerebral blood flow (nitrous oxide) in seven patients with essential hypertension were made before and one hour after apresoline® (10–20 mg.). Arterial pressure had stabilized at the lowest level for ten minutes or had begun to rise at the time of the second flow measurement. Mean changes of this group were: Mean arterial pressure 144 to 113 mm. Hg, cerebral blood flow 56 to 57 cc./100 gm. brain/minute, cerebral vascular resistance (pressure/flow) 2.8 to 2.1, cerebral oxygen uptake 3.6 to 3.2 cc./100 gm. brain/minute, arterial carbon dioxide tension 44 to 38 mm. Hg, jugular venous oxygen content 11.7 to 12.5 volumes, jugular oxygen saturation 63 to 67 per cent, jugular pH 7.35 to 7.40, jugular oxygen tension 36 to 34 mm. Hg, the latter assumed to represent

cerebral oxygen tension. The significant changes were the reductions in pressure, resistance and arterial carbon dioxide tension ($p < 0.02$). These data indicate that 1-hydrazinopathalazine reduced the increased tone in the vessels of the brain to the extent that cerebral blood flow, cerebral oxygen uptake and cerebral oxygen tension were unchanged in these patients at the time of the greatest hypotensive effect.

ROLE OF LIVER IN THYROID HORMONE METABOLISM AS STUDIED BY RADIOACTIVE IODINE IN SPLENIC AUTOTRANSPLANTS IN RATS. *M. W. Hamolsky, M.D., Z. S. Gierlach, M.D. and A. L. Botkin, M.D. (introduced by A. S. Freedberg, M.D.)* (From the Beth Israel Hospital, and Harvard Medical School, Boston, Mass., and the Army Medical Research Laboratory, Fort Knox, Ky.)

The nature of the role of the liver in the metabolism of thyroid hormone remains unclear. The effect of pre-portal transplantation of the thyroid on plasma levels of protein-bound radioactive iodine (PBI^{131}) following I^{131} injection has been studied as a measure of removal of endogenously labelled thyroid hormone by the interposed liver. Five groups of male Sprague-Dawley rats were studied: (I) sham-operated; (II) thyroidectomized; (III) thyroidectomized with gland transplanted to axillary muscle; (IV) and (V) thyroidectomized with gland transplanted to a splenic pouch. Group II animals showed the classical "flattening" of the weight curve post-thyroidectomy. All others followed weight curves comparable to controls, indicating that pre-portal transplantation did not effect athyreosis. The presence of functioning transplants (in 100 per cent of transplant animals) was followed at intervals by external gamma ray counting. At thirty-five to thirty-nine days postoperatively in Groups I–IV and one year postoperatively in Group V the plasma PBI^{131} was determined twenty-four hours follow-I^{131} injection. The values were: controls, 29.9 ± 8.2 per cent; axillary transplants, 23.2 ± 2.9 per cent; thyroidectomized, 3.8 ± 1.6 per cent; splenic transplants (with no residual thyroid demonstrable by G.M. tube scanning at sacrifice), 12.2 ± 5.4 per cent. The data are consistent with partial hepatic removal or inactivation of thyroid hormone under these conditions. No evidence was found of adenoma formation, hyperplasia or hyperfunction in the transplants by histologic study, radioautography and determination of I^{131} uptake and conversion to an organic-bound state.

RENAL RESISTANCES IN NORMOTENSIVE AND HYPERTENSIVE INDIVIDUALS. *J. F. Harris, M.D., M. Wilson, M.D.* and R. H. Lyons, M.D.* (From the State Univ. of New York, College of Medicine, Dept. Medicine, Univ. Hospital of the Good Shepherd, Syracuse, N. Y.)

Renal resistances to blood flow were estimated by the method of Gomez in six hypertensive and seven normotensive individuals immediately before and after autonomic blockade by tetraethyl ammonium. The purpose was to differentiate those effects upon the kidney circulation produced by sudden drop in blood pressure from the effects of uncomplicated autonomic blockade. Peripheral vasodilatation was promoted by heating to minimize the blood pressure drop after TEA. Renal clearances of insulin and paraaminohippurate were determined during seven fifteen-minute periods, the first three periods being the patient's own control. TEA, 500 mg., was then administered intravenously for the first "blockade" period, and an additional 300 mg. were given for a second period. The final two periods served as a recovery phase. The results indicated that renal resistances were not decreased after autonomic blockade but were occasionally increased markedly. When autonomic blockade could be produced without blood pressure drop, renal clearances and calculated resistances did not change. When blood pressure fell after TEA, renal clearances also fell. It would appear that either TEA failed to block the autonomic control of renal vasculature or that the kidney was free of autonomic control under the conditions of this study.

MECHANISMS OF MUSCLE PAIN. *T. H. Holmes, M.D. and T. L. Dorpat, M.D.** (From the Univ. of Washington School of Medicine, Seattle, Wash.)

Pain and tenderness predictably occur during sustained and intermittent contractions of forearm skeletal muscles performed with circulation intact and are qualitatively identical with ischemic muscle pain. The threshold and intensity of pain and endurance of contraction are directly related to the contraction strength. With a strong and sustained contraction they are of similar magnitude both with circulation intact and occluded. With circulation intact,

progressively weaker sustained contractions are associated with longer endurance, higher pain thresholds and lower pain intensities than observed in similar experiments with occluded circulation. In rhythmic exercises with intact blood flow endurance is greater, pain threshold higher and pain intensity lower than with sustained contractions of similar strength. Data from experiments in which muscle temperature was used as an index of blood flow indicate that tonically contracted muscles are relatively ischemic, the degree of ischemia being proportional to the contraction strength. Hyperemia follows strong contractions and occurs during the rest pauses of rhythmic exercises. Return of the lowered muscle pain threshold to control-resting levels parallels the rate of recovery from fatigue and is proportional to the magnitude of the post-contraction blood flow. It is postulated that during the period of relative ischemia which accompanies contracting skeletal muscles there are produced noxious metabolites (Factor P of Lewis) capable of engendering pain. The accumulation of these substances in concentrations sufficient to exceed the pain threshold depends on the form, intensity and duration of contraction.

DEUTERIUM OXIDE AND TOTAL BODY WATER IN EDEMATOUS SUBJECTS. *W. W. Hurst, M.D.*, Portland, Ore. *and F. R. Schemm, M.D.*, Great Falls, Mont.

Total body water was determined in four normal individuals after oral administration of deuterium oxide and subsequently repeated in each after intravenous infusion. In terms of per cent body weight, the variation of total body water per individual did not exceed 2 per cent between the two modes of administration. Seven edematous subjects, five with congestive heart failure and two with chronic glomerulonephritis, were studied after oral administration of deuterium oxide. Fifteen hours were allowed for distribution. That equilibrium was reached was verified in four, in whom blood and chest or abdominal fluid samples were obtained simultaneously at the close of the time periods. The urine volume and its concentration of deuterium oxide were obtained in each instance during the procedure. The average urine loss of deuterium was 3 per cent of the injected dose and the maximum loss was 6 per cent. The volumes were repeated after edema was removed (average of twelve days; range of eight to twenty-one days). The average weight loss was 8 kg., and the average volume loss when each was corrected for excretion during the test period was 7.7 L. The results of this study indicate that oral administration of deuterium oxide is satisfactory. Since a prolonged period of time is required for distribution of the agent in edematous subjects, correction for its urinary loss is desirable.

A DEXTROROTATORY UROBILIN FROM FECES FOLLOWING ANTIBIOTIC THERAPY. *G. W. James, M.D., A. Anderson, M.D.* and V. Wilkerson, M.D.** (From the Laboratories for Clinical Investigation, Dept. of Medicine, Medical College of Virginia, Richmond, Va.)

Stercobilin, strongly levorotatory, isolated from feces by Watson and urobilin IX, *a*, optically inactive, prepared from mesobilirubinogen synthetically, have been thoroughly described. A dextrorotatory urobilin from infected bile, and in feces of one patient following oral aureomycin has been reported but not isolated in quantities for adequate study. From patients with various hemolytic anemias, stercobilin was isolated. Then aureomycin or terramycin was given for several days. When the Ehrlich reaction had returned, a crystalline dextrorotatory urobilin was regularly obtained from the feces in large quantities. In one patient with N^{15} labelled red cells, the isotope content of stercobilin and *d*-urobilin was the same indicating a common source. *d*-Urobilin was present in the feces for as long as two months after the antibiotics had been discontinued. During chloromycetin administration only stercobilin was obtained. *d*-Urobilin possesses some of the chemical and physical properties of both urobilin IX, *a*, and stercobilin. Two crystal forms have been observed. The chemical reactions are more similar to those of urobilin IX, *a*. The Ehrlich reaction, both quantitatively and qualitatively, is identical with stercobilinogen, and *d*-urobilinogen after the Terwen procedure is extractable with petroleum ether. Other properties, its significance, and possible modes of origin will be discussed.

PROPOSED SCHEME FOR COMBINED ANTIBIOTIC ACTION. *E. Jawetz, M.D.* (From the Divisions of Microbiology, Medicine and Pediatrics, Univ. of California, School of Medicine, San Francisco, Calif.)

Antibiotic synergism and antagonism have been demonstrated *in vitro* in infections of experimental animals and in some human infectious diseases. Synergism is defined here as the ability of a pair of drugs to produce a more rapid rate of early bactericidal action, to kill greater numbers of bacteria *in vitro* and exhibit greater therapeutic action than could be expected from the mere summation of single drug effects. Laboratory experiments suggest that fixed "synergistic" or "antagonistic" pairs of drugs do not exist. Combined antibiotic action is a function of the micro-organisms' behavior toward the single antimicrobial agents making up the pair. A given drug pair may be synergistic against one organism, antagonistic against another. Based on the above definition for synergism, available data are compatible with the following scheme for combined antibiotic action: Antibiotics fall into two distinct groups (I) Penicillin, streptomycin, bacitracin, neomycin; (II) aureomycin, chloramphenicol, terramycin. Drugs of group I are often synergistic with each other, occasionally indifferent, never antagonistic. Drugs of group II are not synergistic with, or antagonistic to, each other, but are often additive. Group II drugs are capable of antagonizing group I agents acting on group I-susceptible organisms. Conversely, group II drugs may be synergistic with group I when acting on group I-resistant bacteria. Experimental clinical observations supporting this scheme will be presented.

IDIOPATHIC CONGENITAL HYPOPROTHROMBINEMIA: COMPARATIVE EFFECTS OF PLASMA, WATER SOLUBLE VITAMIN K, FAT SOLUBLE VITAMIN K_1 OXIDE AND EMULSION OF VITAMIN K_1. *B. K. Johnson, M.D.* and W. B. Fronmeyer, Jr., M.D.* (From the Dept. of Medicine, Medical College of Alabama, Birmingham, Ala.)

Since none of the ten reported cases of idiopathic congenital hypoprothrombinemia received single large doses of fat soluble vitamin K_1 oxide or vitamin K_1 emulsion, it was desirable to determine the effect of these and other substances in such a patient. A constant prothrombin deficiency was demonstrated in the patient's plasma by accepted laboratory procedures which showed that the prolonged prothrombin time (29–35 seconds) was not due to a deficiency or unreactivity of thromboplastinogenase, thromboplastinogen, accelerator globulin, fibrinogen, Platelet Factor Number II or Factor VII. A circulating anticoagulant could not be demonstrated and liver function studies were normal. All therapeutic test substances were given intravenously. Separate administration of seven-day old and one-day old plasma in amounts of 425 ml. each promptly reduced the prothrombin time to twenty seconds; 300 mg. of water soluble vitamin K were without prothrombic effect. One gm. of fat soluble vitamin K_1 oxide resulted in immediate prolongation of the prothrombin time to fifty-nine seconds without subsequent reduction below twenty-nine seconds; 600 mg. of emulsified vitamin K_1 gave similar results. It is concluded that true idiopathic congenital hypoprothrombinemia does not respond to the vitamin K preparations tested. This fact serves as another differential point between acquired and congenital hypoprothrombinemia of idiopathic nature.

RED CELL, PLASMA AND MUSCLE COMPOSITION IN THIRTY HUMAN SUBJECTS. *H. G. Keitel, M.D., H. Jones, M.D. and H. Berman, M.D.* (*introduced by P. J. Culver, M.D.*). (From the Dept. of Pediatrics, Harvard Medical School, and the Burnham Memorial Hospital, Mass. General Hospital, Boston, Mass.)

Plasma, red cell and muscle samples from fifteen male and fifteen female surgical patients with non-electrolyte diseases were analyzed for sodium, potassium, chloride, water and phosphorus. Muscle cells contained, on the average, 158 mEq. of K/kg. water and red cells 140 mEq. of K/kg. water, as compared to 107 mEq. in the average body cell as estimated from measurement of the total body water and potassium and the inulin measured extracellular fluid space. The data show an absence of a relation between (1) the plasma K content and the cell K content, and (2) the serum sodium plus potassium content and the cell sodium plus potassium content. These data are discussed in light of present day concepts of acid base and osmotic equilibria.

TOTAL BODY AND RED CELL POTASSIUM CHANGES IN POTASSIUM DEFICIENT PATIENTS. *H. G. Keitel, M.D., H. Jones, M.D. and E. A. MacLachlan, M.D.* (*introduced by P. J. Culver, M.D.*) (From the Dept. of Pediatrics, Harvard Medical School, and the Burnham Memorial Hospital, Mass. General Hospital, Boston, Mass.)

Because of the frequent discrepancy between the serum potassium concentration and the total body potassium content, an attempt was made to study the red cell potassium concentration in various conditions associated with potassium deficiency. Potassium balances were determined in nine potassium deficient patients with diabetic acidosis, gastric alkalosis or other metabolic disorders. The red cell K was determined before and after K therapy. The data to be presented show that the red cell K changes bear a close relationship to the total body K changes.

IMPROVEMENT IN CONGESTIVE HEART FAILURE FOLLOWING INTRAVENOUS HEXAMETHONIUM. *R. T. Kelley, M.D.,* T. F. Higgins, M.D.,* J. C. Rose, M.D.* and E. D. Freis, M.D.* (From the Georgetown Univ. Medical Center, Washington, D. C.)

Hypotensive doses of hexamethonium were administered intravenously to eighteen patients with different types of heart disease in various stages of failure. In fifteen patients the effect on the venous pressure, arm to tongue circulation time, vital capacity and the degree of orthopnea were observed. Cardiac catheterization studies were performed in three additional cases. In all cases with an elevated venous pressure there was a significant fall following hexamethonium, the range being from 40 to 133 mm. H_2O (mean 82 mm.). Of twelve patients with an initial arm-tongue circulation time in excess of twenty seconds eight showed a reduction ranging from 26 to 54 per cent (mean 42 per cent). In eight patients with orthopnea there was marked improvement in five. Catheterization studies showed a significant fall in right auricular and pulmonary arterial pressures accompanied by marked symptomatic improvement. Clinically in the long-term therapy of severe hypertension using hexamethonium it has been observed that congestive heart failure when present is easier to control, and in occasional cases it has been possible to discontinue digitalis and mercurial diuretics. It is suggested that hexamethonium by reducing the total peripheral resistance and possibly by redistribution of blood volume may interrupt the vicious cycle of heart failure.

BALLISTOCARDIOGRAPHIC RESPONSE TO "DEPRESSOR" DRUGS: 1-HYDRAZINOPHTHALAZINE, VERATRONE, HEXAMETHONIUM, PRISCOLINE, REGITINE AND SODIUM AMYTAL. *R. C. Kory, M.D., D. C. Roehm, M.D.* and G. R. Meneely, M.D.* (From the Research Laboratory, Thayer Veterans Administration Hospital, and Vanderbilt Univ., School of Medicine, Nashville, Tenn.)

This study concerns the ballistocardiographic and blood pressure responses of hypertensive patients to parenteral administration, in acute experiments, of six drugs used in hypertension principally for their vascular effect rather than for any direct action upon the heart. Each drug proved capable of producing a striking reversion of abnormal ballistocardiographic patterns toward normal and of increasing cardiac output in certain patients. Usually but not invariably the ballistocardiographic improvements paralleled the hypotensive response. However, priscoline,® a vasodilator, often improved the ballistocardiogram without lowering the blood pressure. Every patient showed both favorable blood pressure and ballistocardiographic response to at least one drug, but no drug was maximally effective in all patients. Since in sustained hypertension many mechanisms may be operative and since the modes of action of these drugs differ widely, comparison of their effects on the individual may reveal predominant hypertensive mechanisms and aid in selection of effective therapy for the patient.

CHANGES IN WHITE BLOOD CELL COUNTS AFTER ADMINISTRATION OF CORTISONE ACETATE TO HEALTHY AMBULATORY INDIVIDUALS. *H. J. Kowalski, M.D., W. E. Reynolds, M.D.* and D. Rutstein, M.D.* (From the Dept. of Preventive Medicine, Harvard University Medical School, Boston, Mass.)

Increased adrenal cortical activity is associated with leukocytosis, neutrophilia, lymphopenia and eosinopenia. Similar but variable effects have been noted after the administration of cortisone acetate. This study confirms and extends early unpublished observations that healthy ambulatory individuals have greater increases in neutrophil counts after intramuscular cortisone than after oral cortisone, and that these are associated with pain on ambulation and tenderness at the site of injection. Each of eight ambulatory subjects received in random order at intervals of at least two days single doses of 50 mg. oral cortisone, 50 mg. intramuscular cortisone in 2 ml. of vehicle and 2 ml. of the vehicle as a control. White blood cell and differential

counts were made frequently during a twenty-four-hour period after each treatment. When compared with response to injection of the vehicle, the oral cortisone was followed by an increase in the neutrophils and decreases in lymphocytes and eosinophils, but no relative change in total white cell count. However, intramuscular cortisone was followed by a greater and more prolonged increase in the neutrophil count, a marked rise in total white cell count but no appreciable change in lymphocyte and eosinophil counts. The rise in neutrophil and total white blood cell counts after intramuscular cortisone was roughly paralleled in time and magnitude by discomfort at the site of injection. It is suggested that the changes noted after oral cortisone are specific pharmacologic effects of the drug but that the changes after intramuscular cortisone are due at least in part to irritation at the injection site.

Effect of Belladonna Alkaloids on Pyloric Obstruction. *P. Kramer, M.D. and S. C. Crocker, M.D.** (From the Evan Memorial, Boston, Mass., and Medical Service, Cushing Veterans Administration Hospital, Framingham, Mass.)

Belladonna alkaloids are frequently prescribed in the treatment of patients with pyloric obstruction due to chronic duodenal ulcer. The usefulness of these agents in pyloric obstruction is debatable. Gastric evacuation in patients with partial pyloric obstruction was studied in two series of patients by two different methods. Each of fifteen patients was given a barium meal and studied fluoroscopically and radiologically on two occasions within a period of a week. One of these tests served as a control study; a therapeutic dose of atropine, bellafoline,® or tincture of belladonna was given fifteen to thirty minutes before the second test. In ten of the fifteen patients gastric retention was increased by more than 25 per cent following medication. Two patients with less than 5 per cent five-hour retention in the control test manifested 100 per cent five-hour retention following belladonna alkaloids. Because x-ray examination provides only limited information, another series of twelve patients with pyloric obstruction was studied by the phenol red dye dilution technic to determine the rate of gastric secretion and evacuation. Atropine sulfate was administered in therapeutic doses sufficient to cause dryness of the mouth. Atropine produced a 50 per cent reduction in the rate of gastric evacuation as well as in the rate of gastric secretion. In some patients the reduction in rate of gastric evacuation was much more pronounced than the reduction in secretion.

Use of Oral High Fat, High Calorie Emulsion for Total Feeding. *W. J. Kuhl, M.D., M. I. Grossman, M.D.* and C. F. Consolazio, M.D.** (From the U. S. Army Medical Nutrition Laboratory, and the Hektoen Institute for Medical Research Chicago, Ill.)

The maintenance of body weight, positive nitrogen balance and an adequate caloric, mineral and vitamin intake while restricted to a liquid diet has been achieved only with difficulty in the past. Because of the high caloric value of fat, a high fat, high calorie liquid diet containing 4,400 cal. in 1,400 ml. was constituted, using 1,000 ml. of a 40 per cent fat emulsion with 100 gm. of protein supplement, 100 gm. of dextrose and adequate quantities of minerals and vitamins. This was administered as the sole source of feeding to six patients with weight loss following fracture of the mandible with wiring, for periods of from twelve to twenty-four days. All patients gained weight and were maintained in positive nitrogen balance. Weekly fasting blood studies revealed no increase in total fat, neutral fat or phospholipid. The basal metabolic rate remained within normal limits but R. Q. decreased or remained low in all patients. Although there was an increase in fecal fat excretion, the per cent of ingested fat excreted was not remarkably elevated. Urine urobilinogen excretion remained within normal limits. There was no consistent change in serum total protein, albumin, globulin, NPN or fasting blood sugar. Urinary ketones were only occasionally detectable. This study is being extended to a larger group of patients.

Use of ACTH and Adrenocortical Hormone Therapy for Protection Against Operative Trauma. *L. H. Kyle, M.D., W. P. Walsh, M.D.* and P. D. Doolan, M.D.* (From the Dept. of Medicine, Georgetown Univ., School of Medicine, and the Georgetown Univ. Hospital, Washington, D. C.)

Adrenocorticotropic hormone, cortisone and adrenal extract have been used extensively in disease states entirely unrelated to endocrine dysfunction. This report deals with clinical and metabolic changes which accompany the more specific application of these substances to patients with endocrine disease. Included in the

study are two patients with hypopituitarism, one with chronic adrenal insufficiency complicated by pregnancy, one with Cushing's syndrome due to an adrenal tumor and one with hypoglycemia resulting from hyperinsulinism. Surgical trauma in patients with hypopituitarism is well tolerated if the patient is given ACTH prior to surgery or treated with large amounts of cortical extract at the time of operation. Marked eosinopenia accompanies either form of treatment but increased nitrogen excretion appears to be dependent upon adequate preoperative protein stores. With the use of adrenal extract and cortisone, delivery in a pregnant Addisonian may be as uneventful as in uncomplicated pregnancy. Administration of large doses of cortical extract at the time of surgery and use of cortisone postoperatively make it possible safely to effect removal of a functioning adrenal tumor despite the presence of contralateral adrenal atrophy. The rise in blood sugar which follows a short period of ACTH therapy in hyperinsulinism allows surgical exploration without undue worry regarding the blood sugar level at the time of operation. These data are presented to illustrate the value of the newer hormonal preparations in such conditions as required their logical application. Such treatment is of especial value in permitting severe surgical trauma in a group of patients notorious for their poor response to stress.

PROTECTION OF TUBERCULIN HYPERSENSITIVE CELLS FROM TOXIC ACTION OF PPD BY CORTISONE IN TISSUE CULTURE. *R. H. Leahy, M.D.* and H. R. Morgan, M.D.* (From the Univ. of Rochester, School of Medicine and Dentistry, and Strong Memorial Hospital, Rochester, N. Y.)

Previous investigators have demonstrated that ACTH or cortisone will inhibit the development of lesions in experimental allergic diseases in animals; this might be due to suppression of: (1) humoral antibody formation, (2) tissue response to injury or (3) damage to capillaries accompanying such reactions. It was decided to investigate the response of isolated tissues in culture. Splenic tissue from tuberculin hypersensitive guinea pigs was selected for these experiments, since Rich had demonstrated the cytotoxic action of tuberculin upon macrophages from such tissue. The roller tube method of tissue culture was used with a fluid medium to which was added: (1) cortisone acetate suspension, or (2) PPD or (3) both cortisone acetate and PPD. For the first twenty-four hours culture tubes received plain nutrient medium or the cortisone-containing medium, depending on their subsequent experimental conditions. These media were replaced by nutrient containing PPD or nutrient containing both PPD and cortisone. The cytotoxic action of PPD was observed in the absence of cortisone. In the presence of cortisone the cytotoxic action of PPD was inhibited. These findings indicate that cortisone acts directly on tuberculin hypersensitive cells *in vitro* to protect them from the cytotoxic action of PPD.

EFFECT OF COMBINED PENICILLIN AND AUREOMYCIN THERAPY IN PNEUMOCOCCIC INFECTIONS OF MICE. *M. H. Lepper, M.D., G. G. Jackson, M.D.* and H. F. Dowling, M.D.* (From the Univ. of Illinois, College of Medicine, Chicago, Ill.)

Aureomycin has been shown to be antagonistic to the antibacterial activity of penicillin *in vitro* and in some experimental infections when the two agents are used simultaneously. We found in the treatment of patients with pneumococcal meningitis that treatment with penicillin plus aureomycin was inferior to penicillin alone. A uniformly fatal infection in mice was established with pneumococcus Type I and therapeutic experiments performed. A combination of aureomycin and penicillin given immediately before infection was more effective than either agent alone when a near-optimal dose was used. However, if aureomycin was administered in an inadequate amount for four hours preceding a single PD_{50} dose of penicillin the therapeutic result was much poorer than the same amount of penicillin alone. The apparent antagonism was not observed with a similarly protective dose of penicillin alone or the combination of drugs given at twenty-four-hour intervals or if repository penicillin was used. Antagonism or potentiation of antibacterial activity in a uniform infection varied with experimental conditions. Translation of these data to clinical use of antibiotic combinations will be discussed.

EVALUATION OF LEFT AND OF RIGHT VENTRICULAR FUNCTION IN HEART FAILURE. *B. M. Lewis, M.D., F. W. Haynes, M.D.,* H. E. J. Houssay, M.D.* and L. Dexter, M.D.* (From the Medical Clinic, Peter Bent Brigham Hospital, and Dept. of Medicine, Harvard Medical School, Boston, Mass.)

The function of the two ventricles has been studied separately during exercise in eight pa-

tients with hypertension or aortic valve lesions in whom cardiac output and right auricular pressure were normal at rest. In five with mild symptoms, pulmonary "capillary" ("PC") pressure (an index of left ventricular diastolic pressure) was normal at rest but on exercise rose abnormally although both cardiac output and right auricular pressures responded normally. In three patients with moderate to severe symptoms "PC" pressure was elevated at rest and rose still further on exertion. The response of cardiac output and right auricular pressure on exercise was normal in one. The second showed a normal cardiac output but a high right auricular pressure, while the third, in gross congestive failure, had a high right auricular pressure with no significant increase in cardiac output. These data demonstrate (1) cardiovascular disease to the point of congestive failure with normal resting cardiac outputs and right auricular pressures, (2) the detection of early abnormalities of the left ventricle by measuring "PC" pressure on exertion and (3) disease affecting primarily the left ventricle causing abnormalities of its function while right ventricular function is apparently still normal.

SPLENIC HYPERFUNCTION IN SICKLE CELL ANEMIA. *H. Lichtman, M.D.,* H. Shapiro, M.D.,* V. Ginsberg, M.D. and J. Watson, M.D.* (From the State Univ. of New York at New York City, College of Medicine, Brooklyn, N. Y.)

Of seventy-nine cases of sickle cell anemia studied in a fifty-five year period nine had enlarged spleens. Of these three with unusually severe anemia and one with persistent leukopenia were thought to have splenic hyperfunction. Aspirations of enlarged spleens showed a two- to thirteen-fold increase of irreversibly sickled cells compared to peripheral blood. The average hemoglobin in sickle cell anemia patients without palpable spleen was 8½ gm. per cent. One patient, age ten, with a hemoglobin of 3.5 gm. per cent had a spleen weighing 1,300 gm. removed at operation. Postoperatively, the hemoglobin levelled off at 10 gm. per cent coincident with dramatic clinical improvement. The patient's red blood cells, transfused into a normal recipient, showed a cell survival curve with two components. Half the cells were destroyed in six days and the remainder within twenty-seven days. Since the patient had a reticulocyte count of 50 to 70 per cent before operation, there was an opportunity to study the reticulocyte survival in the normal recipient. The transfused reticulocytes disappeared (presumably matured) within four days. Normal blood transfused into the patient before operation had a survival of only fourteen days, although in other cases of sickle cell anemia the survival of normal cells is 120 days. The short survival of normal cells indicates that this patient had an additional abnormal extrinsic mechanism, as is seen in splenic hyperfunction. Cell survival studies postoperatively of normal transfused red blood cells in this patient indicate a much longer survival.

EFFECT OF CHLOROMYCETIN UPON ERYTHROPIESIS. *W. Lindau, M.D.* (From the V. A. Hospital, Coral Gables, Fla.)

Chloromycetin was given for thirty days to eight hospital patients, seven of whom suffered from chronic degenerative diseases but were in a steady state of their disease. In two of the three patients in whom there were significant findings a second course of chloromycetin was given after sufficient time had elapsed for the hemograms to return to their previous level. Bone marrow aspiration, red blood counts, hemoglobin, hematocrits, white blood counts and differentials were performed at the beginning and completion of each course of chloromycetin. Hematocrits were done at weekly intervals. In three of the eight patients there was arrest of erythropoietic maturation, with an average decrease in the hematocrit of 8.6 per cent (10, 8 8). Bone marrow examination revealed a definite decrease in the orthochromatic normoblasts. After the hematocrit had returned to the base line a second thirty-day course of chloromycetin was given to two of these three patients. Again the hematocrit fell. Upon discontinuation of the medication the hematocrit level again returned to the control value. It is concluded that a thirty-day course of chloromycetin is capable of causing a significant anemia in some individuals.

TREATMENT OF ULCERATIVE COLITIS: COMBINED THERAPY BY INTERNIST AND PSYCHIATRIST. *S. H. Lorber, M.D., H. Shay, M.D.* and E. Baum, M.D.** (From the Temple Univ. School of Medicine, and Temple Univ. Hospital, Phila., Pa.)

Results are reported in the treatment of fourteen patients with ulcerative colitis employing the combined efforts of internist and psychiatrist. Nine patients were severely ill, one was moderately ill and four were classified as mild. Medical management followed all accepted

principles. Initial psychotherapy consisted of reassurance and encouragement. Later, daily interviews were initiated by the internist. Occasional interviews were conducted by the psychiatrist who also reviewed the material obtained by the internist. The psychiatrist then guided the therapeutic efforts of the internist who attempted to develop the patient's understanding of the emotional factors involved. Upon discharge from the hospital patients who made a good psychologic adjustment were followed by the internist. If emotional problems remained unresolved, both internist and psychiatrist treated the patient. All patients but two responded well to this regimen. Eight patients who have been followed for over one year are completely rehabilitated. The encouraging results obtained both with respect to immediate and long-term management, not only lend additional support to the concept of a disturbed psyche in the etiology and recurrences of ulcerative colitis but also point to the value of teamwork between internist and psychiatrist in the treatment of this disease.

EFFECT OF SPLANCHNICECTOMY ON THE HYPOGLYCEMIC AND EOSINOPENIC RESPONSE TO INSULIN. *H. F. Loyke, M.D.* and S. W. Hoobler, M.D.* (From the Dept. of Medicine and Section Neurosurgery, Department of Surgery, Univ. of Michigan Medical School, Ann Arbor, Mich.)

Six patients were studied before, seven days and three months after operation (splanchnicectomy and ganglionectomy D_{12}–D_9 or above). No differences were noted except for insulin resistance and failure of eosinophils to fall in the early postoperative period. Patients whose blood pressure had stabilized at one to four years postoperatively were divided into good and poor result categories, depending on a drop of 40 mm. or more in systolic blood pressure. Six of nine poor result patients had an eosinopenia of 40 per cent or greater to the insulin test. Thirteen of sixteen good result patients had less than 40 per cent eosinopenia, and eight of them showed no reduction. The differences were statistically significant. The hypoglycemic stimulus was of the same magnitude in both groups but the initial level of eosinophils was slightly, but not significantly, lower in the good result group. It is concluded that the response of the pituitary adrenal system to insulin hypoglycemia is significantly altered in patients who have a good result from splanchnicectomy. A transient but definite blood pressure lowering occurred during recovery from hypoglycemia and during a time when the serum K was lowered. Whether acute shifts in K concentration in the fluid compartments of the body or decreased cerebral metabolism may be responsible for these hypotensive effects is under further investigation.

COMPARATIVE STUDY OF CARDIOVASCULAR RESPONSES IN THE NORMOTENSIVE AND HYPERTENSIVE INDIVIDUAL UNDER VARYING STAGES OF HYDRATION. *R. H. Lyons, M.D. and J. F. Harris, M.D.* (From the Dept. of Medicine, State Univ. of New York, College of Medicine, Syracuse, N. Y.)

Five hypertensive and six normotensive individuals were studied during stages of normal hydration, overhydration and dehydration for changes in the cardiovascular response. Changes in renal function, heart size, venous pressure, resting blood pressure and the response to autonomic blockade with tetraethyl ammonium were compared. The glomerular filtration rate and renal plasma flow, after acute dehydration, fell proportionately to the degree of dehydration and to a similar degree in both groups. Venous pressure tended to increase with overhydration, and decreased after dehydration similarly. Changes in heart size on x-ray were produced to a comparable degree in both the hypertensive and the normotensive. After desalting, mean blood pressure remained the same in the normotensive but fell in the hypertensive. Autonomic blockade, however, produced large drops in blood pressure in both groups during dehydration. Shock levels were produced as easily in the normotensive as in the hypertensive. This would imply that either the normotensive depends upon humoral factors in blood pressure, comparable to the hypertensive; or that the marked drop in blood pressure after autonomic blockade results in both groups from embarrassment of the circulation due to the direct effects of dehydration.

PULMONARY "CAPILLARY" PRESSURE FIXATION AS AN INDICATION OF ADVANCED PULMONARY VASCULAR CHANGES IN MITRAL STENOSIS. *M. C. McCord, M.D., S. G. Blount, Jr., M.D.* and L. L. Anderson, M.D.** (From the Univ. of Colorado, Dept. of Medicine, Denver, Colo.)

The presence of advanced changes of the pulmonary vascular bed existing as a co-obstruction with mitral stenosis may markedly limit the benefit derived from mitral commissurotomy.

Therefore, twenty patients with mitral stenosis were studied by cardiac catheterization in an attempt to predict the presence and severity of such changes. Failure of the pulmonary "capillary" pressure to rise more than 20 per cent on exercise is believed to be an indication of significant pulmonary vascular disease. The patients exhibiting a rise in the mean pulmonary "capillary" pressure of 20 per cent or more were characterized clinically by episodes of acute paroxysmal dyspnea and pulmonary edema. The patients showing a rise of less than 20 per cent were those presenting symptoms of right ventricular decompensation. Correlation of the pulmonary "capillary" pressure change with microscopic examination of the pulmonary vessels was made when possible by biopsy or autopsy examination. The change in the pulmonary "capillary" pressure on exercise appears to be a more specific indication of pulmonary vascular bed disease than are the "capillary" pressure levels *per se*. It is concluded that relative fixation of the pulmonary "capillary" pressure is an indication of advanced pulmonary vascular changes and should be an important consideration in selecting patients for mitral commissurotomy.

CONGENITAL ABSENCE OF THE RIGHT PULMONARY ARTERY DIAGNOSED BY ANGIOCARDIOGRAPHY AND CARDIORESPIRATORY STUDIES. *I. M. Madoff, M.D., E. A. Gaensler, M.D. and J. W. Strieder, (introduced by E. H. Kass, M.D.).* (From the Thorndike Memorial Laboratory, Boston City Hospital and Harvard Medical School, Massachusetts Memorial Hospitals and Boston Univ. School of Medicine, Boston, Mass.)

Diagnosis of congenital absence of the right pulmonary artery in the presence of aerated lungs was made by angiocardiography in a fifteen year old girl. This anomaly has been reported six times since 1868 and has never been recognized during life. There were apparently no other associated congenital cardiovascular defects. Physical examination was normal and the patient was asymptomatic. Bronchography and bronchoscopy revealed some narrowing of the right upper lobe bronchus as the only abnormality. Pulmonary function studies showed the maximun. breathing capacity, residual volume and total capacity, air flow velocity, intrapulmonary mixing and arterial oxygen saturation to be normal. During bronchospirometry with room air the right lung showed normal ventilation but did not participate in oxygen uptake. By inducing hypoxia and supplying room air to the left lung and oxygen to the right lung the right bronchial arterial supply could be made responsible for eighteen per cent of the total oxygen uptake. The entire right cardiac output entered the left lung. By application of the Fick principle to one lung it was estimated that 15 per cent of the left cardiac output entered the right lung. This additional load on the left side of the heart was thought insufficient to warrant removal of the functionless lung.

NEW EOSINOPHIL TEST FOR ADRENOCORTICAL RESPONSE AND ITS APPLICATIONS. *B. F. Massell, M.D., H. S. Rubin, M.D.,* J. D. Knoblock, M.D.,* and T. Ito,** (From the House of the Good Samaritan, Boston, Mass.)

The percentage fall in eosinophils four hours after a single intramuscular injection of ACTH was found to be an unsatisfactory measure of adrenocortical response because of wide variations in percentage change and only slight increase in mean fall with increased ACTH. When a given amount of ACTH is administered in six equally divided hourly intramuscular injections, there is a progressive and consistent decrease in eosinophils reaching a maximum seven hours after the initial injection. This new method of administering ACTH was utilized as a test for adrenocortical response. Compared to the four-hour eosinophil test it has these advantages: the decrease in eosinophils is consistent; the variations in end point with any given amount of ACTH are relatively small; there is a close correlation between the mean fall and the total amount of ACTH administered. To apply this test a standard curve has been constructed with a single lot of ACTH relating percentage eosinophil change to total amount of hormone. The sensitivity of this test allows a number of applications including the assay of ACTH in human subjects, the study of adrenocortical responsiveness in various diseases and under the influence of various drugs. Some of these applications will be demonstrated.

MICROSCOPIC PATHOLOGIC CHANGES IN TISSUES OF RATS AND DOGS GIVEN HYDRAZINE DERIVATIVES OF ISONICOTINIC ACID. *C. Mermod, M.D.,* P. L. Stefko, M.D.,* M. D. Roe, M.D.,* and W. M. Benson, M.D.* (From the Pharmacology Dept., Hoffmann-La Roche, Inc., Nutley, N. J.)

A recent report on the pharmacology and toxicology of the hydrazine derivatives of isonicotinic acid by Benson, Stefko and Roe described the gross pathology of rats and dogs which received rimifon® (isonicotinic acid hydrazide) and marsilid® (1-isonicotinyl-2-isopropyl hydrazine). The drugs were administered over a period of thirteen weeks at several dose levels and by various routes to these animals. This paper presents the microscopic pathologic changes of the organs. The tissues of the animals on the higher dosages gave evidence of destruction of red blood cells, engorgement of the spleen and concomitant bone marrow hyperplasia with extramedullary hematopoiesis in the case of marsilid. Some of the rats on rimifon showed low grade parenchymatous degenerative changes in the liver and kidneys. This was less marked in the organs of rats which received marsilid. On the other hand, dogs which received marsilid showed heavy deposits of blood pigment in the liver and moderate toxic effects in the kidneys. At the lower doses, which are comparable to those used clinically, lesser degrees of pathologic changes were noted. Whereas rimifon induced less hematopoietic activity in both rats and dogs, it exhibited slightly greater toxicity on the livers of both species. Renal changes were noted in dogs which received both drugs but not in rats which received marsilid. The degree of reversibility of the bone marrow, hepatic, splenic and renal changes after cessation of treatment is under investigation. In two dogs which were sacrificed two weeks after the termination of marsilid administration the tissues showed little abnormality.

EXPERIENCE WITH DIRNATE, AN ORAL DIURETIC AGENT. *J. P. Merrill, M.D.* (From the Dept. of Medicine, Harvard Medical School and Medical Service, Peter Bent Brigham Hospital, Boston, Mass.)

Dirnate,® an unsubstituted sulfonamide, can be administered orally and appears to be nontoxic. As a carbonic anhydrase inhibitor, it may prohibit the exchange of Na for hydrogen ions thus promoting sodium diuresis. Of fifteen patients with edema, including congestive heart failure, Kimmelstiel-Wilson syndrome and nephrotic syndrome, eight have responded with a significant sodium diuresis. The results have been compared with mercuhydrin injection. The data indicate that dirnate may result in a significant increase in urinary volume and sodium excretion in patients whose control urinary pH is low with a large amount of titratable acid. Initially there is a marked rise in urine pH, concentrations of chloride and potassium, a decrease in ammonia and titratable acid. Continued administration shows a decreasing effect with a return to control levels of all values within three days. An increase in urinary potassium excretion may persist or rarely be the cation maximally increased initially. In congestive failure without renal insufficiency the diuretic response was less marked than with mercurials. When response to both drugs occurred, the urinary Na/Cl ratios were invariably less than one with mercury and greater with dirnate. Of clinical importance were the significant increments of urinary Na resulting from dirnate administration in edematous uremics whose residual tubular function permitted acidification of the urine. In such patients mercurials were ineffective.

OBSERVATIONS ON THE ROLE OF UREA IN UREMIA. *J. P. Merrill, M.D.,* M. Legrain, M.D.* and R. Hoigne, M.D.** (From the Dept. of Medicine, Harvard Medical School and Medical Service, Peter Bent Brigham Hospital, Boston, Mass.)

In the treatment of uremia with the artificial kidney a period of oliguria following dialysis has been noted in some cases. This occurs without changes in vascular or renal hemodynamics during the procedure. Post-dialysis oliguria was manifest in about 25 per cent of chronic nephritics treated. The duration is three to five days, and the volume of urine averaged about 50 per cent of the pre-dialysis output. Patients with hypertension and vascular disease (Group A) were most affected, while polyuric, normotensive uremics (Group B) showed no change. The oliguria appeared to be related to decrease in the total serum osmolarity resulting largely from decrements of blood urea. Concomitant decreases of urine urea occurred. In most instances both plasma and urine concentrations of sodium and chloride increased. This oliguria has been prevented in the Group A patients by dialysis against high urea baths. The lack of change in blood urea does not impair the excellent clinical response. These observations confirm the impression that urea plays little role in the clinical toxicity of uremia and that elevated blood urea levels may serve a useful function in maintaining urine volume of the uremic

patient. That urea, a non-resorbed substance, is more important in this regard than resorbable osmotically active substances is indicated by the occurrence of oliguria in spite of hypertonic sodium chloride loading.

USE OF THE NEWER AUTONOMIC BLOCKING AGENTS IN THE STUDY AND TREATMENT OF PERIPHERAL VASCULAR DISEASE. *M. Moser, M.D., D. Watkins, M.D.,* N. Morris, M.D.,* J. A. Orbison, M.D.* and T. W. Mattingly, M.D.* (From the Walter Reed Army Hospital, Washington, D. C.)

The effect of long and short term administration of an oral peripheral adrenergic blocking agent, dibenzyline,® and parenteral ganglionic blocking agents, penta- and hexamethonium, was determined in fifty-five patients with various forms of peripheral vascular disease. Plethysmographic and skin temperature studies were done in warm, cool and cold environments. Results were compared with similar tests employing both oral and intra-arterial priscoline.® Results indicate that intravenous hexamethonium® in 50 mg. doses produces a rapid increase in blood flow and skin temperature in both the upper and lower extremities that is comparable and occasionally exceeds the results obtained after sympathectomy. The increase in flow is greater than that produced by 50 to 75 mg. of intra-arterial priscoline. Hexamethonium in these doses was found to be impractical for routine clinical use because of severe side effects. It was of great value, however, in the treatment of hospitalized patients who were bedridden with acute occlusive arterial disorders, thrombophlebitis or severe chronic occlusive vascular disease, and was the most satisfactory agent found for use in releasing vascular tone and predicting the outcome of proposed sympathectomy. Dibenzyline in single oral doses of 2 mg./kg. produced increases in blood flow and skin temperatures in the upper extremities which, although not as great as those produced by hexamethonium, were much more prolonged. The effect of this dosage on the lower extremities was not significant. Chronic administration of oral dibenzyline in doses of 20 to 60 mg. q.i.d. to forty-five patients demonstrated that it was more effective than oral priscoline and of great value in the treatment of Raynaud's disease, other vasospastic disorders, hyperhidrosis and causalgic states. The results obtained in occlusive vascular disease were encouraging in only a few patients. Side effects were not severe; tolerance to the drug developed in six patients.

ANTAGONISM BETWEEN HEPARIN AND ADRENOCORTICAL EOSINOPENIA *in vitro* AND *in vivo*. *R. C. Muehrcke, M.D.,* J. L. Lewis, M.D.,* J. Peters, M.D.* and R. M. Kark, M.D.* (From the Dept. of Medicine and the Research and Educational Hospitals of the Univ. Illinois, College of Medicine, Chicago, Ill.)

Many investigators, including the authors, have tried in vain to reproduce adrenocortical eosinopenia in the test tube, using heparinized or oxalated blood. We recently found statistically significant, reproducable adrenocortical eosinopenia *in vitro* when *defibrinated* human blood was incubated sterilely with cortisone or compound F. This eosinopenia was blocked by adding heparin to defibrinated blood before adding cortisone. Various substances (inert particulate matter; adrenocorticotropin; insulin; steroidal substances such as DOCA and digitalis; histamine and epinephrine; protamine sulfate, toluidin blue, etc.,) were tested in the system for eosinopenic activity and for blocking of cortisone, with no effect. Morphologic changes occur only in cortisone incubated eosinophils. Differential counts of cortisone incubated defibrinated blood show changes which mimic closely those found in synovial fluid after intra-articular injection of cortisone (Duff et al.). Tremendous amounts of intravenous heparin block adrenocorticotropin eosinopenia in man but coagulation remains prolonged (Godlowski). We found equivocal blocking of adrenocorticotropin eosinopenia *in vivo* with small amounts of heparin. Results support the concept of specific peripheral effects of cortisone. The heparin blocking is not related to anticoagulant action. Speculations on the relationship of mucopolysaccharide polymerization to the system will be presented.

HEMODYNAMIC CHANGES IN HUMANS FOLLOWING INDUCTION OF LOW AND HIGH SPINAL ANESTHESIA. II. SPLANCHNIC BLOOD FLOW, OXYGEN EXTRACTION AND CONSUMPTION. *R. P. Mueller, M.D.,* R. B. Lynn, M.D.* and S. M. Sancetta, M.D.* (From the Division of City Hospital, Dept. of Public Health and Welfare, Cleveland, Ohio.)

The effect of spinal anesthesia on the splanchnic blood flow, oxygen extraction and consump-

tion and hepatic portal resistance was investigated in ten waking patients who had undergone no surgical procedure. The direct Fick principle was employed. Anesthetic levels ranging from T10 to T2 were achieved. The following alterations from the basal state have been observed. There is a decrease in the brachial arterial pressure, the estimated hepatic blood flow and the oxygen content of hepatic venous blood, an increase in the brachial arterial hepatic venous oxygen difference, and a relative increase in splanchnic oxygen extraction. These changes become intensified as higher dermatomic levels are anesthetized. The level of anesthesia does not affect the calculated splanchnic oxygen consumption and the hepatic portal resistance which are not significantly altered from the basal control levels. Evidence is presented to indicate that the percentile contribution of the hepatic blood flow to the total cardiac output is not altered by the severe hypotension and reduced total cardiac output which follow blockade of the preganglionic sympathetic outflow above the level of the fourth thoracic segment.

EFFECTS OF HUMAN PLASMA ON RABBIT BLOOD CELLS. *C. W. Mushett, M.D.,* E. H. Reisner, Jr. M.D. and L. Weiner, M.D.** (From the Merck Institute of Therapeutic Research, Rahway, N. J. and the Division of Hematology, Dept. of Medicine, New York Univ. Post Graduate Medical School, New York, N. Y.)

The intravenous injection of rabbits with serum and plasma from normal and thrombocytopenic humans, as well as reconstituted lyophilized human plasma, resulted in a prompt thrombocytopenia, hemolytic anemia and lymphocytopenia. These effects appear to be related to dosage which if sufficiently large caused death of the animals. Rabbits were not protected against the effects of human plasma by prior treatment with ACTH. Heating of plasma to destroy complement did not alter its action. The response of the rabbit to human plasma or serum does not appear to be merely a foreign protein reaction, since dog plasma in comparable dosage had no effect. Agglutination of rabbit red cells and platelets by human plasma could be demonstrated *in vitro*. Following repeated intravenous injections of human plasma over several weeks there was a significant decrease in the susceptibility of red cells from the recipient rabbit to *in vitro* agglutination by the same plasma. Agglutinates of rabbit platelets resulting from contact with human plasma were not removed by glass-wool filters employed in Moolten's method.

CORRELATION STUDIES ON TESTS FOR HISTOPLASMOSIS WITH PULMONARY CALCIFICATION AND TUBERCULIN TESTS. *R. L. Overman, M.D.,* V. F. Colville, M.D.* and C. J. D. Zarafonetis, M.D.* (From the Temple Univ. School of Medicine and Hospitals, Philadelphia, Pa.)

Previous investigations have disclosed a high order of correlation between the incidence of pulmonary calcification and positive histoplasmin skin tests in tuberculin negative individuals. The present study is an attempt to determine the degree of correlation with a complement-fixation test for histoplasmosis. Blood specimens were drawn and histoplasmin skin tests applied to student nurses and laboratory personnel who had had recent chest photofluorograms (70 mm.) and tuberculin skin tests. A single lot of histoplasmin (mycelial filtrate) was used for the skin tests. The complement-fixing antigen consisted of a suspension of killed yeast-phase organisms. It was standardized through titration against a known positive serum. The method of preparation of the antigen and the complement-fixation procedure employed have been previously described. Of 282 subjects tested twenty-six gave positive histoplasmin skin tests and five had complement-fixing antibodies in low titer. The positive complement-fixation tests occurred only in sera from individuals with positive histoplasmin skin tests. Similar studies are being carried out in older age groups. These preliminary results suggest that the complement-fixation test with yeast-phase antigen is less sensitive than the histoplasmin skin test. The degree of correlation of the skin tests and complement-fixation results with pulmonary calcification will be discussed.

ABNORMAL ADJUSTMENT TO DIETARY MANIPULATIONS IN EXPERIMENTAL MOUSE OBESITY. *J. A. Owen, Jr., M.D.,* L. J. Falk, Jr., M.D.,* K. R. Crispell, M.D. and W. Parson, M.D.* (From the Dept. of Medicine, Univ. of Virginia, Charlottesville, Va.)

Little is understood of homeostatic mechanisms resulting in adjustment to dietary manipulations in normal animals with maintenance of relatively constant body weight. This problem has been studied by offering normal and obese mice diets of varying caloric dilution. Young

female mice of the dba strain were injected with 20 mg. (MLD_{60}) of gold thioglucose, as solganol-B® in aqueous solution. A significant degree of obesity developed in 54 per cent of the survivors. On *ad libitum* feedings of standard laboratory diet the obesity reached a relatively static phase in three months. The diet was diluted to 50 per cent by weight by admixture with kaolin. It was found that uninjected non-obese mice of the same age increased their intake of diluted food and were able to maintain their weight. The obese animals failed strikingly to make this adjustment and lost weight; when regular diet was resumed their food intake increased above previous levels and they again became obese. Gold-injected non-obese mice did not differ from controls when their diets were diluted. Alterations in consistency of diet also resulted in significantly different food consumption and weight curves. It is concluded that the obese animal does not respond to dietary dilution with sufficient increase in food intake to maintain body weight.

ABNORMALITIES IN EXCRETION OF WATER AND SODIUM IN "COMPENSATED" CIRRHOSIS OF THE LIVER. *S. Papper, M.D. and J. D. Rosenbaum, M.D.* (From the Boston City Hospital, Thorndike Memorial Laboratory, Boston, Mass.)

Five normal men and six patients with clinically "compensated" portal cirrhosis had no evidence of cumulative fluid retention when maintained for two weeks on a diet providing 225 mEq. of sodium chloride daily. While recumbent after breakfast each subject drank sufficient water to establish and maintain for two hours a load of 20 ml./kg. During this period and the next four hours renal excretory rates of water, sodium, chloride and potassium, and endogenous creatinine clearance were measured and compared with the antecedent nocturnal rates. When dietary sodium intake was 35 mEq. daily, only minor abnormalities in water and electrolyte excretion were demonstrable in two of the patients. However, when 225 mEq. of sodium were ingested daily, four of the six failed to attain normal maximal rates of water and sodium excretion and manifested an abnormal diurnal rhythm of sodium excretion. The other two patients were undergoing spontaneous diuresis during the period of study. They excreted sodium at high rates but their maximal rates of water excretion were probably significantly below those observed in the normal subjects with similar rates of sodium excretion. This suggests that antidiuretic hormone activity may be increased even when latent edema is being delivered.

EFFECT OF SYRUP OF LICORICE ON SODIUM AND POTASSIUM BALANCE IN PATIENTS WITH ADDISON'S DISEASE. *A. E. Parrish, M.D. and L. K. Alpert, M.D.* (From the Veterans Administration Hospital and George Washington Univ. School of Medicine, Washington, D. C.)

Three patients with known Addison's disease and one with a renal salt-losing defect were studied to determine the effect of syrup of licorice on their disease. In each patient the sodium and potassium intake was measured and sodium and potassium excretion in the urine, feces and gastric contents was determined. Serum electrolytes were measured at the same time. After a control period of five to six days the patients were given 30 cc. of syrup of licorice four times a day and the balance study continued for another five to seven days. Two of the patients exhibited loss of sodium and retention of potassium during the control period, which was reversed when they received syrup of licorice. In one patient there was sodium loss and potassium retention throughout both the control and experimental periods. In the fourth patient there was potassium retention during the control period and loss during the time of licorice administration, but the sodium balance varied in both a positive and negative manner during both periods. Similar studies were made on normal and adrenalectomized rats. It was found that there was sodium retention and potassium loss during the period that they were on syrup of licorice.

EFFECT OF PURIFIED DIET, THIAMINE AND OTHER VITAMINS ON THE CLINICAL SIGNS OF WERNICKE'S SYNDROME. *G. B. Phillips, M.D.,* M. Victor, M.D.,* R. D. Adams, M.D.* and C. S. Davidson, M.D.* (From the Boston City Hospital and Harvard Medical School, Boston, Mass.)

Six patients with Wernicke's syndrome, characterized by ophthalmoplegia, nystagmus, ataxia and mental disturbances were given on admission to the hospital a diet consisting solely of glucose and minerals for from three to ten days. At appropriate intervals specific vitamins were added. Prior to thiamine administration the ophthalmoplegia progressed and the ataxia re-

mained unchanged, despite alcohol withdrawal, bed rest and the addition of other vitamins (riboflavin, niacin, pyridoxine, calcium pantothenate, folic acid, vitamin B_{12} and ascorbic acid). The nystagmus decreased only in association with an increase in ocular paralysis. When thiamine alone was added (initially 5 to 200 mg. parenterally), the ophthalmoplegia improved in from one and one-quarter to six hours. The nystagmus and ataxia diminished more gradually while thiamine administration was continued. Mental disturbances were present in five patients on admission but showed little if any improvement on the purified diet regardless of therapy or subsequently when a regular hospital diet was given for from nine to twenty-eight days. One patient while on the purified diet developed mental disturbances which disappeared four days after institution of the regular hospital diet. It is concluded that the ophthalmoplegia, nystagmus and ataxia of Wernicke's syndrome were reversed by the administration of thiamine alone.

DUAL DISPLACEMENT AND VELOCITY BALLISTOCARDIOGRAPH APPARATUS. *L. Pordy, M.D., K. Chesky, M.D., A. M. Master, M.D., R. Taymor, M.D. and M. Moser, M.D.* (From the Cardiographic Laboratory, The Mount Sinai Hospital, New York, N. Y.)

Ballistocardiography has become a practical routine clinical procedure through introduction of the simple direct body type of apparatus by Dock and Taubman. The value of this procedure has been established empirically by the *qualitative* appearance of the component waves of the ballistocardiographic tracings. One of us (L. P.) has devised a standardized dual ballistocardiographic apparatus, modified after Dock, for recording simultaneous or successive displacement (photoelectric) and velocity (electromagnetic) tracings with a single setting of the transmitting bar on the shins. Simultaneous ballistocardiographs taken in this manner show marked qualitative difference between the photoelectric and electromagnetic records, particularly in regard to the I waves and the diastolic waves. The technic for establishing reproducible standardized conditions for ballistocardiographic tracings is described. The apparatus permits introduction of a respiratory filter for photoelectric tracings as well as simultaneous electrocardiograms for timing purposes by a simple switch arrangement.

EFFECT OF DOCA ON ELECTROLYTE BALANCE IN NORMAL SUBJECTS AND ITS RELATION TO SODIUM INGESTION. *A. S. Relman, M.D. and W. B. Schwartz, M.D.* (From the Dept. of Medicine, Boston Univ. School of Medicine and the Evans Memorial, Mass. Memorial Hospitals, the Dept. of Medicine, Tufts College Medical School and the New England Center Hospital, Boston, Mass.)

The influence of three different levels of salt intake (500 mM., 200 mM. and 15 mM. per day) on the metabolic effects of desoxycorticosterone acetate has been investigated in normal young adults by means of the balance technic. Intramuscular administration of 20 mg. of DOCA per day produced an average daily potassium loss of 21 mEq. in excess of nitrogen in the six subjects on high or normal salt intakes, with a tendency for the potassium loss to decrease after the first few days of treatment. In the three subjects on the low salt intake there was little or no potassium loss in response to the same dose of DOCA. Sodium retention was proportional to the sodium intake, decreased with time, and bore no relationship to potassium loss in the subjects on normal or high salt intakes. A significant decrease in serum potassium concentration was observed in these two groups. The excretion of ammonia increased slightly but there was no change in the excretion of titratable acid, phosphorus or nitrogen, and no change in serum bicarbonate. Calculation of internal balances on the basis of chloride space showed a small intracellular shift of sodium in the high and normal salt intake groups.

PROLONGATION OF ELECTRICAL SYSTOLE (Q-T INTERVAL) AS ADDED CRITERION IN THE LEVY ANOXIA TEST. *D. C. Roehm, M.D.,* R. C. Kory, M.D. and G. R. Meneely, M.D.* (From the Research Laboratory and Radioisotope Unit, Thayer Veterans Administration Hospital and Vanderbilt Univ. School of Medicine, Nashville, Tenn.)

Although anoxia is one of the causes of prolongation of the Q-T interval, this change has not been used for evaluation of the Levy anoxia test. Twelve patients with angina pectoris and positive anoxia tests by Levy's criteria had a mean maximal increase of 0.040 ± 0.011 seconds in the Q-T interval corrected for rate (Bazett) contrasted with a mean maximal increase of 0.014 ± 0.009 seconds in nineteen

normal volunteer subjects. Seven patients with strong clinical evidence of angina pectoris but with negative Levy tests and ten patients with chest pain considered non-cardiac in origin also with negative Levy tests were investigated. Neither group showed statistically significant Q-T prolongation during anoxia. When the maximal Q-T_e increase was compared with the initial Q-T_e duration, a relationship became apparent which may be expressed thus: K = initial Q-T_e + 2.6 × maximal Q-T_e increase. If the normal upper limit of K is taken as 0.480 seconds, all the patients with positive Levy tests and most of the patients with convincing evidence of angina pectoris fall above this value whereas all the normal controls and most of the patients with chest pain of non-cardiac origin are below.

EFFECTS OF CONTROLLED VARIATIONS IN RATE, STROKE AND MINUTE VOLUME ON VASCULAR DYNAMICS IN DOGS, USING A MECHANICAL LEFT VENTRICLE. *J. C. Rose, M.D.,* C. A. Hufnagel, M.D.,* J. F. Gillespie, M.D.,* H. P. Brodia, M.D.* and E. D. Freis.* (From the Georgetown Univ. Medical Center, Washington, D. C.)

An all plastic diaphragm pump has been successfully substituted for the left ventricle in dogs. The pump permits independent control of rate through a range from 35 to 280 strokes per minute and of output from 0.2 to 6.0 L. per minute at any of the above rates, unaltered by peripheral resistance. Blood was collected from the left auricle and pumped proximally and distally into the descending thoracic aorta; the right heart remained intact. The effects of alterations in rate and stroke volume within and beyond the physiologic ranges were determined. Quantitative relationships were obtained between these controlled variables (rate and output) and the pressure pulses measured simultaneously in the iliac artery, inferior vena cava and pulmonary artery as well as the blood flow returning to the pump. There was a constant relationship linear within limits between minute pump output and the pressure levels in the cava and pulmonary artery as well as in the iliac artery. In the absence of direct interference with peripheral resistance, pressures in all parts of the system and the pulmonary venous return were observed to be direct functions of pump minute volume. At a constant minute volume variations in rate and stroke volume affected primarily pulse pressure in the arterial system.

STUDIES ON THE ANTIGENIC PROPERTIES OF HUMAN LYMPHOCYTES. *M. Saint-Paul, M.D.,* J. McNulty, M.D.* and W. Moloney, M.D.* (From the Boston City Hospital, Boston, Mass.)

Employing lymphocytes obtained from patients with lymphatic leukemia, the following investigations were carried out: (1) In testing a large number of normal human sera and sera from patients with various disorders, no lymphocyte agglutinins were found; (2) sera of rabbits, guinea pigs and sheep contained no agglutinins for human lymphocytes. In a large series of random dog sera 10 per cent of the sera agglutinated human lymphocytes in low titer; (3) human lymphocytes were investigated for content of A and B agglutinogen. Direct agglutination and absorption methods failed to reveal the presence of these antigens; (4) potent human lymphocyte agglutinating serum was produced in rabbits (1:1000). Activity was not enhanced by serum or albumin systems; trypsin and Coomb's effects were not observed. Antihuman lymphocyte serum also agglutinated human neutrophils, red cells and platelets but the antilymphocyte agglutinins were of much higher titer. Differential absorption resulted in strong antilymphocyte agglutinins remaining in the serum. Potent antihuman lymphocyte serum, absorbed with red cells on injection into guinea pigs and a dog, did not cause a fall in any cellular elements. Antihuman platelet, neutrophil and red cell serum, produced by immunization of rabbits, also agglutinated lymphocytes but only in low titer.

PIGMENTS OF THE BILE IN LIVER AND GALLBLADDER DISEASE. *V. M. Sborov, M.D. and W. S. Sharon, M.D.** (From the Walter Reed Army Medical Center, Washington, D. C.)

This study was undertaken to clarify the relationships of urobilin, urobilinogen and bilirubin of the bile in disease of the liver and biliary tract. Bile was obtained by non-surgical drainage in four groups of patients: (1) no liver or gallbladder disease, (2) acute viral hepatitis, (3) chronic viral hepatitis and cirrhosis and (4) cholelithiasis. "A" plus "B" bile (common duct and gallbladder) was separated from "C" bile (hepatic) and the urobilinogen, urobilin and bilirubin measured. In all cases the urobilinogen, urobilin and bilirubin of the "A" plus "B" bile were found to be higher than the "C" fraction.

Urobilinogen levels were found to be lowest in acute viral hepatitis and highest in the "A" plus "B" bile of patients with cholelithiasis. The bilirubin of the hepatic bile was low in the cases of acute viral hepatitis but was not significantly different from that in patients with no hepatic or biliary tract disease. In patients receiving aureomycin or terramycin therapy the urobilinogen content of all samples was markedly reduced while the bilirubin values were unchanged. The amount of urobilin in the hepatic bile was five to ten times higher than the native urobilinogen in all cases. This probably means that most of the bile pigment is absorbed from the gut as urobilin and is excreted unchanged in the bile.

THE BALLISTOCARDIOGRAM IN PERSONS OVER EIGHTY-FIVE YEARS OF AGE. *J. A. Schack, M.D.,* O. Tannenbaum, M.D., L. Friedfeld, M.D. and H. Vesell, M.D.* (From the Beth Israel Hospital and the Home of Old Israel, New York, N. Y.)

Ballistocardiograms were obtained from nineteen persons, ten male and nine female, over eighty-five years old. The apparatus was of the electromagnetic (variable reductance) direct type. All patients were ambulatory and had been studied clinically to evaluate cardiac and peripheral vascular status. There were four Grade I, two Grade II, ten Grade III and three Grade IV ballistocardiograms in this group. In the persons with Grades I and II ballistocardiograms the 12 lead electrocardiogram was normal in two instances. One of the persons whose ballistocardiogram was Grade IV had a normal electrocardiogram. Two Grade I and one Grade II ballistocardiogram occurred in the presence of intraventricular block. Six individuals demonstrated normal teleoroentgenograms. In these individuals the ballistocardiogram was Grade I or Grade II in four. There was only one instance of a diastolic blood pressure exceeding 90 mm. Hg. The ballistocardiogram of this individual was Grade I. Three instances of systolic blood pressure of 140 mm. Hg or less were recorded. Two of these individuals demonstrated Grade I ballistocardiograms. The data indicate that with advancing years the ballistocardiogram tends to be abnormal, the abnormality deriving from both cardiac and extracardiac sources. Apparently, in the aged the distortion of the ballistocardiogram by extracardiac forces (chiefly rigidity of the aorta) may be marked.

STUDIES ON THE PHYSIOLOGY OF AWARENESS: DIFFERENTIAL INFLUENCE OF COLOR ON ARTERIAL OXYGEN SATURATION. *R. A. Schneider, M.D. and J. W. L. Doust, M.D.* (From the Institute of Psychiatry, Maudsley Hospital, London, England.)

Forty-nine healthy control subjects and thirty-eight patients with such psychiatric disorders as neurosis, depression, schizophrenia and epilepsy were investigated oximetrically to assess their arterial oxygen saturation. Resting levels were determined and then a series of cards on which were superimposed solid circles of different colors were presented individually. The hues represented were white, blue, orange, green, purple, red, black and yellow. The subject was requested to look at each card and after an exposure of five seconds a spectroscopic oximetric reading was taken. The cards were presented in the order listed, the white card being repeated at the end. Finally all cards were displayed simultaneously and the subject asked to rank them for preference. The results indicated that all colors save white induced significantly differential anoxemic levels as compared with resting values in both control and patient groups. The greatest oximetric depression occurred with black and, of the chromatic colors, was most pronounced with red and orange, least with blue and green, yellow falling in between. The relationship between these results and the position of such hues in the spectrum appeared significant ($p < .05$). Rank order of color preference for both groups of subjects correlated with oximetric values to give a *rho* for the chromatic hues of 0.43.

PHARMACOLOGY AND CLINICAL TRIAL OF A MICROCRYSTALLINE CHLOROMYCETIN SUSPENSION. *E. B. Schoenbach, M.D.* (From the State Univ. Medical Center and the Maimonides Hospital of Brooklyn, N. Y.)

Microcrystalline chloromycetin, suspended in saline (1 gm./2 ml.), passes freely through an 18 or 20 gauge needle. When introduced intramuscularly, a single dose of 2 gm. caused no irritation or pain. Within an hour after 50 mg./kg. were administered blood serum levels were approximately 10 μg./ml., rose to 20 to 40 μg./ml. during the ensuing three hours and persisted at this concentration for nine to twelve hours. Significant levels were noted for more than twenty-four hours. Spinal fluid concentra-

tion averaged 50 per cent of that in the blood. Thirty to 40 per cent of the dose was detected in the urine within twenty-four hours. Repeated dosage at twelve-hour intervals of 50 mg./kg. for four to eighteen days resulted in minimum concentrations of 20 to 80 μg./ml. in the serum and 10 to 40 μg./ml. in the spinal fluid. These levels exceeded those obtained when the same daily dosage was administered orally. No local or systemic reactions were observed when the intramuscular route was employed for the treatment of thirty-eight infants or postoperative patients who could not tolerate oral medication. Twenty-one of these patients had a purulent meningitis (15 H. influenzae, 2 staphylococcal, 1 meningococcal and 1 S. typhimurium). The microcrystalline suspension was a useful and effective preparation when parenteral therapy with chloromycetin was indicated.

ALTERATIONS IN FLUID AND ELECTROLYTE BALANCE ASSOCIATED WITH STRESSFUL LIFE SITUATIONS. *W. W. Schottstaedt, M.D.* and L. E. Hinkle, M.D.* (From the New York Hospital-Cornell Medical Center, New York, N. Y.)

It is known that stressful situations may lead to significant alterations in fluid and electrolyte balance in man and experimental animals. To investigate this phenomenon further, serial studies were made of plasma volume, blood electrolytes and urinary excretion rates of Na, K, Cl and H_2O under control conditions and during exposure to stress induced by discussion of pertinent personal conflicts. Healthy persons and subjects with cardiac disease and migraine were studied. It was found that exposure to such stress led to significant changes in plasma volume and serum concentration of Na and Cl accompanied by changes in the rate of excretion of Na, Cl and H_2O. Changes of the magnitude of 20 per cent have been observed in plasma volume and serum Na concentration. It is evident that internal fluid and electrolyte balance may be significantly altered during bodily adaptation to stressful situations. The relevance of these findings to the occurrence of cardiac failure is under investigation.

ROLE OF CARBONIC ANHYDRASE IN RENAL TUBULAR REABSORPTION OF BICARBONATE. *W. B. Schwartz, M.D., L. E. Danzig, M.D.,* and A. S. Relman, M.D.* (From the Dept. of Medicine, Tufts College Medical School and the New England Center Hospital; the Dept. of Medicine, Boston Univ. School of Medicine, and the Evans Memorial, Mass. Memorial Hospitals, Boston, Mass.)

The mechanism of bicarbonate reabsorption has been reinvestigated, using as a tool the potent carbonic anhydrase inhibitor, 2-acetylamino, 5-sulfonamide, 1,3,4-thiodiazole (6063). 0.1 to 500 mg./kg. of this drug have been administered intravenously to unanesthetized dogs whose serum bicarbonate values had been set, by previous administration of acid or alkali, at levels ranging from extreme acidosis to mild alkalosis. Immediately upon administration of 6063 there was a significant increase in bicarbonate excretion, the magnitude of which appeared to depend in part on the dose. Severely acidotic animals responded less than those moderately acidotic. The maximal inhibition of bicarbonate reabsorption occurred in the alkalotic dogs, with a diversion into the urine of up to 60 per cent of the previously reabsorbed bicarbonate. Calculated urine pCO_2 rose to levels more than three times those existing simultaneously in the plasma. These data imply that carbonic anhydrase activity is a rate-limiting factor in the over-all process through which bicarbonate is reabsorbed. The magnitude of the increase in bicarbonate excretion suggests that 6063 inhibits reabsorption in the proximal tubule.

COMPARATIVE EFFECTIVENESS OF SEVERAL NEW HYPOTENSIVE AGENTS AS DETERMINED BY THEIR ACTION IN EXPERIMENTAL RENAL HYPERTENSION AND IN THE HUMAN PATIENT. *A. P. Shapiro, M.D. and A. Grollman, M.D.** (From the Southwestern Medical School of the Univ. of Texas, Dallas, Texas.)

The reputed effectiveness of newly introduced agents in the treatment of hypertension prompted their evaluation in the experimental hypertensive animal (rat and dog) and in humans. The following drugs were used: 1-hydrazinophthalazine (apresoline®), hexamethonium salts, dibenzylyline and, for comparative purposes, tetraethylammonium chloride. Following intravenous injection of these drugs the blood pressure may fall but the dose required is variable and no consistent correlation exists between the clinical state and the severity of the hypertension and the degree of hypotensive effect elicited. Moreover, one cannot predict which of the drugs is most effective in any given

patient. Side effects and development of tolerance are also unpredictable and interfere with their fullest potentialities as hypotensive agents. A synergistic action between 1-hydrazinophthalazine and hexamethonium could be demonstrated in animal experiments. Improvement in the clinical condition of patients with the malignant phase of hypertension was sometimes observed. However, control studies in these same patients indicate that a variety of non-specific factors may have contributed to this improvement. Their hypotensive action under certain conditions may make these drugs of value as adjuncts to treatment, particularly in the malignant phase; but our results do not support the view that they are primary therapeutic agents.

OSMOTIC BEHAVIOR OF RED CELLS IN HEMOLYTIC PHENOMENA. *J. R. Sharpsteen, Jr., M.D.* (*introduced by S. O. Waife, M.D.*) (From the Dept. of Chronic Diseases of the Chest, Philadelphia General Hospital, and Hahnemann Medical College, Philadelphia, Pa.)

The osmotic pressure of a series of normal bloods was determined by taking the freezing point of the whole blood, plasma, plasma dialysate and cellular dialysate. The pressures were determined by measuring freezing point in a standard chamber using a thermometer which could be read to 0.005°C. Normal and experimental subjects studied were fasting for at least four hours prior to study. In each case a given proportion of cells were hemolyzed and the protein osmotic pressure of the residue was determined. The hemolytic fragility was found to vary directly with the protein content of the cell. An absolute hydrostatic pressure necessary to cause hemolysis was then calculated by adding a constant osmotic pressure found to be that of the diffusible portion of the dialysate. Three cases of acute sickle cell anemia, three cases of acquired hemolytic anemia and one case of congenital hemolytic anemia were studied in the same manner. The hemolytic anemias had elevated osmotic pressures averaging 2 to 4 atmospheres above normal. The sickle cells had an average decrease of 1 to 3 atmospheres. Maximum and minimum normal daily variations were then determined. Predicted results placed three of the above cases within the hemolytic range and each had an elevated icterus index. The remaining cases showed a smaller margin of safety than normal, 0.5 atmospheres as compared to 3.0 atmospheres. There was no laboratory evidence of hemolysis in the remainder. It is suggested that hemolysis in hemolytic anemias is dependent solely on the protein osmotic pressure of the cell and that hemolysis may occur in the cell of increased protein osmotic pressure during extremes of normal daily variation.

COMPENSATORY RENAL ADAPTATION FOLLOWING UNILATERAL NEPHRECTOMY IN MAN. *J. H. Sirota, M.D., L. Narins, M.D.* and G. D. Oppenheimer, M.D.** (From the Depts. of Medicine and Urology, The Mount Sinai Hospital, New York, N. Y.)

Clearances of inulin (C_{IN}), p-aminohippurate (C_{PAH}) and Tm_{PAH} were determined in the separate kidneys of twelve subjects before unilateral nephrectomy and in the remaining kidney at intervals varying from 3 to 631 days after nephrectomy. Only those subjects presenting relatively good function of their diseased kidney were chosen for this study. C_{IN}, C_{PAH} and Tm_{PAH} of the diseased kidneys averaged 38.2, 42.8 and 36.4 per cent, respectively, of the total bilateral values for these functions. In general, compensatory adaptation by the remaining kidney manifested itself by a rapid, moderate rise in C_{PAH} occurring during the first two weeks, a more gradual and less pronounced rise in C_{IN}, and a gradual but marked increase in Tm_{PAH} which attained peak values after several weeks. The maximum increases for the remaining kidney for all the subjects averaged 39.4 per cent for C_{PAH}, 21.2 per cent for C_{IN} and 70.6 per cent for Tm_{PAH}. These represent 81.4 per cent, 73.2 per cent and 106 per cent of the total bilateral prenephrectomy control averages for these respective functions. It is of interest, that in spite of the functional glomerulotubular imbalance (depressed C_{IN}, normal Tm_{PAH}) presented by these patients, they manifest no evidence of salt and water retention.

COMPARATIVE POTENCY OF NEWER ANTICHOLINERGIC DRUGS IN MAN, AS DETERMINED BY A SIGMOID BALLOON TECHNIC. *M. H. Sleisenger, M.D.,* T. P. Almy, M.D., M. Eisenbud, M.D.,* and L. Wallace, M.D.** (From the New York Hospital, Cornell Medical Center, New York, N. Y.)

Clinical use of anticholinergic drugs, heretofore based largely upon animal experimentation, has indicated that many such compounds effec-

tive in animals are inert in man. The action of these agents on the human intestine is readily measured by kymographic tracings obtained following intubation of the sigmoid colon with a distensible balloon. In previous studies, methantheline bromide (banthine®) caused complete abolition of sigmoid contractions whereas atropine produced lesser effects and the older synthetic antispasmodics were inert. The action of seventeen newer synthetic anticholinergic agents has been observed in eighty-eight subjects and compared with that of methantheline bromide. Twelve drugs revealed slight or no effect. Five (SC 3054, SC 3171, SC 3183, SC 3192, and C 5473) produced nearly complete abolition of contractions. All of this group are quaternary amines. In effective doses they frequently produced xerostomia and other atropine-like side effects. Further objective studies of the action of these drugs in human subjects should aid in directing the search for clinically useful anticholinergic agents.

RESPONSE TO PSYCHOLOGIC STRESS IN PERSONS WHO ARE POTENTIALLY HYPERTENSIVE. *M. Sokolow, M.D.,* R. E. Harris, M.D.,* L. G. Carpenter, M.D.,* M. Freedman, M.D.* and S. P. Hunt, M.D.** (From the Division of Medicine and Psychiatry, Univ. California School of Medicine, San Francisco, Calif.)

Investigations of patients with essential hypertension have led us to recognize certain personality and behavior patterns characteristic of the disease. Their relevance for etiology, however, remains obscure. A demonstration that abnormal personality reactions, particularly in situations involving stress, exist before the onset of fixed hypertension would add plausibility to the argument that personality factors play a role in the causal chain of events leading to hypertension. To this end thirty-nine college women who had shown elevations of blood pressure on routine initial physical examinations were matched with thirty-nine controls with low normal pressures. It has been shown that more of the former group will develop hypertension in later life, and hence may be assumed to be "pre-hypertensive." Controlled experimental stress was induced by staging interpersonal situations in which the subjects played assigned roles. One psychodrama involved simple frustration; the second, criticism, rejection and hostility from an authoritative person. Psychologic tests were obtained before and after psychodramas. Behavior during the experimental situations was observed and recorded. A psychiatrist interviewed the students, attempted to identify their characteristic responses to stress and to infer which were pre-hypertensive. The test-interpreters, observers and psychiatrist did not know whether the subjects were pre-hypertensive or control until the data had been analyzed. Most of the procedure showed clearly significant differences between the groups. The pre-hypertensives were typically more hostile and less well controlled than the normals and, in general, less well equipped to cope with experimental stress. Although the etiology of essential hypertension is complex, our data show that the individuals who reacted less adequately to experimentally induced stress were those who demonstrated an elevated blood pressure on the initial college examination and therefore may be presumed to react similarly to other situations of stress and ultimately to develop fixed hypertension.

TREATMENT OF MALIGNANT HYPERTENSION WITH HEXAMETHONIUM BROMIDE. *M. Soklow, M.D., J. Kaufman, M.D.,* G. W. DeLappe, M.D.* and D. DeKruif, M.D.** (From the Division of Medicine, Univ. California, School of Medicine, San Francisco, Calif.)

In our experience papilledema disappeared spontaneously in only three of eighty-eight patients with malignant hypertension treated symptomatically; normal renal function was present in these three. We have treated nine patients with malignant hypertension in the past ten months with hexamethonium bromide subcutaneously. The dose was progressively increased while the patient was in the hospital and varied from 40 to 150 mg. daily. After discharge the patients themselves injected the drug two or three times daily. Significant impairment of renal function was present on admission in six of the nine patients. The therapeutic benefit was striking and has persisted to date (three to six months) in four patients. Rapid relief of severe headache and vomiting, fall in blood pressure, improvement vision in, and loss of papilledema occurred in days to weeks. The remaining five patients (four of whom had severe renal impairment) died, although significant temporary clinical improvement occurred in three. The data indicate that treatment with hexamethonium resulted in striking clinical improvement in four of nine patients with malignant hyper-

tension, despite impaired renal function in three of the four. The period of observation is short but the results to date are encouraging, especially in view of the ominous prognosis for untreated patients.

LONG-ACTING MICROCRYSTALLINE DESOXYCORTICOSTERONE ESTERS IN THE TREATMENT OF ADDISON'S DISEASE. *S. Z. Sorkin, M.D. and L. J. Soffer, M.D.** (From The Mount Sinai Hospital, N. Y.)

Desoxycorticosterone acetate, hitherto the best practical measure in the maintenance therapy of Addison's disease, requires daily injection or hospitalization for implantation. This prompted efforts to obtain a long-acting hormone which could be given by injection at infrequent intervals. Aqueous suspensions of the recently prepared microcrystalline desoxycorticosterone trimethyl acetate and phenyl acetate were used, with oral supplementary sodium chloride, in ten proven cases of Addison's disease. Over sixty injections were given; the patients were treated from three to twelve months. A single injection of 45 to 100 mg. of either ester maintained the patients in good health for four to eight (average 5.5) weeks. The over-all effect —general well being, restoration to useful activity, ability to withstand intercurrent infection —was at least as good as with DCA. There was no serious side effect; excessive rise in blood pressure or fluid retention did not occur; blood electrolytes remained stable. In a few instances early but definite adrenocortical insufficiency was corrected by a single depot-injection of microcrystalline ester which then maintained the patients for more than four weeks. Microcrystalline desoxycorticosterone esters and recent advances facilitating early diagnosis make it possible to treat Addisonian patients who are not in crisis on a completely ambulatory basis and without recourse to daily hormone injections.

THROMBOCYTOASTHENIAS: MULTIPLE SYNDROMES DUE TO QUALITATIVE PLATELET DEFICIENCIES. *M. Stefanini, M.D., L. Solomon, M.D.* and E. P. Santiago, M.D.** (From the New England Center Hospital, Boston, Mass.)

A group of hemorrhagic diatheses has been studied in which thrombocytes are normal in number but appear large, bizarre and hypomotile. Poor clot retraction, slightly deficient prothrombin activity of plasma, incomplete conversion of prothrombin to thrombin during clotting, prolonged bleeding time, increased capillary fragility have been observed singly or in combination, in these patients. These findings, together with the recent characterization of independent factors responsible for the multiple physiologic activities of platelets, appear to indicate that, in pathologic conditions, individual platelet factors may be deficient and therefore individual platelet functions inadequate. *In vivo* transfusion of normal platelets temporarily normalized the hemostatic dysfunction of these patients; *in vitro* the deficient plasma prothrombin or defective prothrombin utilization during clotting or clot retraction could be corrected by the addition of normal human platelets. When platelets isolated from blood of patients with various forms of thrombocytoasthenia were added to platelet-poor native normal plasma, the original defect of the hemostatic mechanism was reproduced. Incubation of normal platelets in serum of such patients failed to modify their morphology and function. These results apparently exclude the role of plasmatic factors in the pathogenesis of thrombocytoasthenia and point to a primary abnormality of platelets.

N,N′DIBENZYLETHYLENEDIAMINE DIPENICILLIN G (DIBENZYL PENICILLIN), AS A PROPHYLACTIC AND THERAPEUTIC AGENT AGAINST GROUP A STREPTOCOCCI. *G. H. Stollerman, M.D. and J. R. Rusoff, M.D. (introduced by C. F. Wilkerson, M.D.)* (From the Irvington House and New York University-Bellevue Medical Center, New York, N. Y.)

N,N′ dibenzylethylenediamine dipenicillin G (dibenzyl® penicillin), a new repository type of penicillin, was administered to a group of 125 children, age six to fourteen, convalescing from rheumatic fever, to determine its possible value as a prophylactic and therapeutic agent against Group A streptococci. Detectable serum levels of penicillin were found for unusually long periods of time following single intramuscular injections. A continuous penicillin level was maintained in patients receiving 300,000 units intramuscularly once weekly and in those receiving 600,000 units once every two weeks. When 1.2 million units were administered, detectable penicillin serum levels were found in 90 per cent of patients three weeks later and 67 per cent at the end of one month. The carrier state was eliminated in all five patients in whom Group A streptococci were found by throat culture prior to therapy. Weekly throat cultures were negative

for Group A streptococci in all treated patients during the seven-month period of study. There were no recurrences of rheumatic fever in the treated group. There was no significant change in the pharyngeal flora at the end of three and six months. Reactions were limited to transient local pain and tenderness at the site of injection and, in two patients, mild urticaria which lasted about forty-eight hours and did not recur when injections were continued.

COMPARISON OF SERUM QUINIDINE CONCENTRATIONS INDUCED BY PARENTERAL AND ORAL COMPOUNDS. *N. J. Sweet, M.D., M. Sokolow, M.D. and M. Masten, M.D.** (From the Univ. of California School of Medicine, and the San Francisco Hospital, Dept. of Public Health, San Francisco, Calif.)

Preliminary studies are presented comparing the serum concentrations produced by one oral and three parenteral quinidine preparations. Solutions of (1) quinidine gluconate (0.8 gm. in 10 cc.), (2) quinidine sulfate (0.6 gm.) in propylene glycol (2 cc.) and (3) quinidine sulfate (0.6 gm.) in urea-antipyrine solution (4 cc.) were given intramuscularly. Quinidine sulfate (0.6 gm.) was given orally. Each dose of these four preparations contained 0.5 gm. of quinidine base. Employing a photo-fluorometric technic, serum quinidine concentrations were determined one-half, one, two and four hours after administration of each drug. This procedure was carried out fifty-five times in thirty-nine patients. Four patients received all preparations at intervals of one week or more. The data indicate that serum quinidine concentrations achieved with a single intramuscular injection of 0.8 gm. of quinidine gluconate are higher and more rapidly reached than those produced by equivalent amounts of oral quinidine sulfate, intramuscular quinidine in propylene glycol or intramuscular quinidine in urea-antipyrine solution. Ten consecutive patients with paroxysmal arrhythmias were treated with a single dose of 0.8 gm. of quinidine gluconate intramuscularly. All converted to sinus rhythm in two hours or less without incident. This group included patients with auricular flutter (2), auricular fibrillation (3), auricular tachycardia (2) and ventricular tachycardia (3).

HEMOLYTIC EFFECT OF X-RADIATION: SURVIVAL OF NORMAL ERYTHROCYTES TRANSFUSED TO IRRADIATED DOGS. *A. N. Swisher, M.D. and F. W. Furth, M.D.* (*introduced by L. E. Young, M.D.*) (From the Univ. of Rochester, School of Medicine and Dentistry, Rochester, N. Y.)

A method of quantitative differential agglutination of dog erythrocytes has been developed. Normal canine erythrocytes have been shown to survive in the normal recipient's circulation for periods of over 100 days. Dogs were exposed to whole body x-irradiation in doses of 450 r to 550 r. Immediately following irradiation, 250 cc. of blood were removed from each animal and 250 cc. of fresh, serologically identifiable, compatible blood were given. The fate of the transfused cells was followed in the post-irradiation period by the technic of differential agglutination. The majority of the dogs became significantly anemic during the subsequent twenty-eight-day period. The rate of disappearance of the autogenous cells was much more rapid than that of the transfused cells during the initial post-irradiation period in most of the anemic dogs; in several, however, an abnormally rapid rate of disappearance of both autogenous and donated cells was observed. A normal rate of disappearance of autogenous and donated cells was demonstrated in animals that developed little or no anemia. These observations suggest that in certain animals a mechanism of red cell destruction is activated during x-irradiation exposure which is not active against normal cells introduced following irradiation. Other exploratory studies on the hemolytic effect of radiation will be cited briefly.

EFFECT OF ADRENOCORTICAL STIMULATION ON THYROID FUNCTION. *D. E. Szilagyi, M.D. and A. B. McGraw, M.D.** (From the Henry Ford Hospital, Detroit, Mich.)

In order to amplify the evidence now available for the explanation of the strikingly favorable results observed by us after the empirical administration of corticotropin in three cases of extremely severe thyrotoxic crisis when all other methods had failed, and also in order to explore certain further possibilities of the clinical usefulness of corticotropin, the following investigations were made. Preparatory to definitive surgical treatment, corticotropin was administered under suitable laboratory control for periods of from two to three weeks as sole therapeutic agent to five patients whose severe thyrotoxicosis had proven resistant to all medical means of

management. At intervals during the period of corticotropin administration the degree of thyroid activity was measured by means of the conventional clinical criteria, by basal metabolic rate, blood cholesterol and protein-bound iodine levels, and by radioiodine uptake and exetion. The effects of corticotropin were variable. All measurements revealed marked decrease of thyroid activity in one case and a moderate decrease in another case. In one case a definite augmentation was noted. In two cases the changes varied from index to index. The radioactive iodine uptake and excretion studies appeared to yield the results most consistent with the general trend of the other measurements and of the clinical course. All cases showed a definite, if at times slight, clinical improvement and all withstood the surgical procedure of radical subtotal thyroidectomy exceptionally well. From a correlation of all the findings it was concluded that corticotropin is beneficial in the preoperative preparation of patients with thyrotoxicosis refractory to conventional medication. It was postulated that the effect of corticotropin is mediated through the anti-stress function of the increased adrenocortical secretory activity and that the depression of thyroid function through diminished TSH secretion is of occasional and minor importance.

EFFECT OF THE CARBONIC ANHYDRASE INHIBITOR, 6063 (2-ACETYLAMINO-1,3,4,THIADIAZOLE-5-SULFONAMIDE), ON RENAL EXCRETION OF WATER AND ELECTROLYTES. *R. C. Taymor, M.D., M. Halpern, M.D.,* and C. K. Friedberg, M.D.* (From the Mount Sinai Hospital, New York, N. Y.)

The carbonic anhydrase inhibitor, 6063, was administered intravenously to two normal subjects and to eight subjects with congestive heart failure, and the effect on plasma electrolytes and on the renal excretion of water and electrolytes was studied. There was a moderate reduction in the carbon dioxide content and a slight lowering of the pH of the blood. Plasma concentrations of sodium, potassium, chloride and phosphorus were not significantly altered. The control urine was acid in eight and slightly alkaline in two subjects. Within one hour after the administration of 6063, the urine became alkaline in all cases. The renal excretion of ammonia was sharply diminished. The control excretion rate of sodium in patients with congestive heart failure was 10.3 μEq./minute on a diet containing between 200 and 500 mg. of sodium per day and reached a mean peak of 148 μEq./minute after 6063. In patients with unrestricted sodium intake the mean control sodium excretion was 133 μEq. with a mean peak of 310 μEq./minute; in the normal subjects, the control excretion rate of sodium was 83.9 μEq. with a rise of 431 μEq./minute after 6063. The mean potassium excretion rate increased from 40.3 to 188 μEq./minute, phosphorus from 346 to 793 μq. per minute, chloride from 47.9 to 95.0 μEq./minute, and bicarbonate from 8.21 to 399 μEq./minute. The electrolyte excretion pattern differed markedly from that observed after a mercurial diuretic. The urine flow increased from 1.58 to 5.02 cc. per minute.

EFFECT OF INFUSING INTERMEDIATES ON BLOOD CONCENTRATIONS OF ALPHA-KETOGLUTARATE AND PYRUVATE IN DOGS. *P. E. Teschan, M.D., D. Seligson, M.D. and G. McCormick, M.D. (introduced by V. M. Sborov, M.D.).* (From the Dept. of Hepatic and Metabolic Diseases, Walter Reed Army Medical Center, Washington, D.C.)

Acetate, ethanol, lactate, alanine, aspartate, ethyl oxalacetate, fumarate, succinate, glutamate and citrate were administered intravenously to dogs. Blood pyruvate and alpha-ketoglutarate were measured by a paper chromatographic method which is accurate and specific (Seligson and Shapiro, 1952). Fifty millimoles of each compound of 150 ml. of solution were infused in thirty minutes. Blood pyruvate and ketoglutarate were measured at 0, 30, 60, 120 and 210 minutes. Acetate infusion produced a fall in pyruvate concentration within thirty minutes, followed by a rise to a peak value at sixty minutes. Ethanol similarly caused an initial lowering of pyruvate which was, however, sustained. A slight rise of ketoglutarate occurred at 30 minutes with the acetate but not with the ethanol infusion. Lactate, alanine, aspartate and asparagine infusions caused a prompt, large elevation of pyruvate with but slight changes in ketoglutarate. However, ethyl oxalacetate, fumarate and succinate caused marked, immediate elevations in both pyruvate and ketoglutarate concentrations. Citrate and glutamate infusions produced a decline in pyruvate concentration in thirty minutes while ketoglutarate simultaneously rose. Some of these responses measured *in vivo* may be explained by known *in vitro* reactions. Application of this method to human patients is being studied.

ANTIPYRETIC ACTION OF AUREOMYCIN. *G. Tillotson, M.D.* and H. S. Ginsberg, M.D.* (From the Depts. of Preventive Medicine and Medicine, School of Medicine, Western Reserve Univ., and the Univ. Hospitals, Cleveland, O.)

Reports that aureomycin favorably influences the course of several viral diseases without evidence that it limits multiplication of the etiologic agents suggested that the action in these instances might be of a non-specific nature. To determine if aureomycin behaves as an antipyretic, its effect on the febrile response of rabbits injected intravenously with influenza virus has been studied. Aureomycin, 25–50 mg. per kg. of body weight, injected intraperitoneally into rabbits reduced rectal temperatures 2° to 6°F. for periods of time ranging up to six hours. Aureomycin given one-half or two hours before and two hours after intravenous injection of influenza A or B virus completely blocked the temperature rise observed in untreated animals. Depression of temperature of rabbits injected with aureomycin and virus was less and of shorter duration than that of animals given aureomycin alone. A single injection of aureomycin 1.5 hours after the administration of influenza virus, at the time when the pyrogenic effect was commencing, blocked any further increase in fever, and temperatures in treated animals returned to normal levels earlier than in controls. This effect of aureomycin was of the same order of magnitude as that produced by aminopyrine when injected one hour after typhoid vaccine.

CHOLINE CONTENT OF MESENTERIC VENOUS BLOOD FROM AN ISOLATED INTESTINAL LOOP AFTER INSTILLATION OF CHOLINE. *J. W. Vester, M.D., J. de la Huerga, M.D.,* M. I. Grossman, M.D.* and H. Popper, M.D.** (From the U. S. Army Medical Nutrition Laboratory, and the Hextoen Institute for Medical Research, Chicago, Ill.)

Previous studies from these laboratories suggested the possibility that choline is absorbed into the mesenteric venous blood as such. A technic was therefore devised to investigate this. A 10 cm. loop of small intestine of a heparinized dog under sodium pentobarbital anesthesia was isolated between occlusive ties and a polyethylene cannula so secured that solutions could be instilled into the gut lumen. The mesenteric vein draining this loop was divided and a two-piece polyethylene cannula inserted into the open ends. Blood flow was thus reëstablished and a known amount of choline was then instilled into the lumen of the intestinal loop. At intervals blood samples were taken from the divided vein cannula in such a way that the amount of blood flowing per unit times could be estimated. Pilot studies to date demonstrate that (1) choline is present in the mesenteric venous blood unchanged, as indicated by chemical and crystallographic studies, (2) at the end of two hours the amount of choline absorbed from the lumen of the gut is 30 to 40 per cent in the case of a 1.0 gm. load and (3) analysis of blood content and remaining intestinal content, together with the estimation of blood flow, will account for 90 per cent of the instilled substance.

ASCORBIC ACID DEFICIENCY IN PERNICIOUS ANEMIA. *R. O. Wallerstein, M.D.,* J. W. Harris, M.D. and G. J. Gabuzda, Jr., M.D.* (From the Boston City Hospital, and Harvard Medical School, Boston, Mass.)

Vitamin C levels were determined in twenty patients with untreated classical pernicious anemia. No patient exhibited clinical signs of scurvy. Peripheral blood or bone marrow buffy coat vitamin C levels were determined in sixteen patients; plasma only was assayed in four patients. In seventeen no vitamin C was present; in three the buffy coat contained 17.0, 22.1 and 11.1 mg./100 gm. In two patients with nutritional megaloblastic anemia and free hydrochloric acid in the gastric contents no vitamin C was found. Two patients with pernicious anemia were given 1 gm. of vitamin C intramuscularly for eleven or more days. One made no hematologic response, the other had a reticulocyte peak of 7.7 per cent without hemoglobin rise or marrow maturation. A third patient who had made a moderate reticulocyte rise to daily injections of 0.33 μg. vitamin B_{12} made a second and greater rise when 1 gm. of vitamin C was given daily intramuscularly and also orally in addition to the vitamin B_{12}. These data suggest that patients with pernicious anemia may have biochemical evidence of severe vitamin C deficiency without signs of clinical scurvy and that vitamin C may play an adjuvant role in hematopoiesis.

TREATMENT OF BARBITURATE POISONING BY HEMODIALYSIS. *W. P. Walsh, M.D.,* L. H. Kyle, M.D., D. P. Doolan, M.D. and H. Jeghers, M.D.*

(From the Dept. of Medicine, Georgetown Univ. School of Medicine and Hospital, Washington, D. C.)

Studies have been conducted to determine the feasibility of use of the artificial kidney in the treatment of barbiturate poisoning. In order to compare the amount of barbiturate removed by hemodialysis with that obtained by normal renal excretion, two patients with chronic uremia were given a therapeutic dose of barbiturate prior to dialysis. Two normal persons were given a similar dose and urinary excretion was measured. It was found that removal of the drug by hemodialysis was much more efficient than that accomplished by renal excretion. To determine the comparable rates of removal of barbiturate, urinary excretion of the drug was measured in three patients with barbiturate poisoning under varying conditions of hydration. Urinary excretion varied between 2 and 13 mg. of barbiturate per hour, the higher values being associated with massive hydration. In a control patient with a comparable blood level of barbiturate who underwent dialysis by the artificial kidney the average removal of barbiturate was 121 mg. per hour. One patient with severe barbiturate poisoning excreted 71 mg. of barbiturate in a urine volume of 1,240 cc. over a period of twelve hours just prior to hemodialysis. After a five-hour dialysis 739 mg. of the drug were found in the bath. In terms of hourly excretion 6.0 mg. were removed by the kidneys and 148.0 mg. by hemodialysis. This patient was completely areflexic and unresponsive to analeptic therapy after thirty-six hours of conservative treatment prior to dialysis but following this procedure she responded readily to picrotoxin. On the basis of these findings it may be concluded that barbiturates are removed at least fifteen to twenty-five times more effectively by hemodialysis than by normal urinary excretion and the use of the artificial kidney is recommended for the treatment of severe barbiturate poisoning.

INFLUENCE OF THE SICKLING PHENOMENON ON THE INCIDENCE AND TYPE OF TUBERCULOSIS. *W. Weiss, M.D.,* S. O. Wolfe, M.D. and W. Stechner, M.D.** (From the Dept. of Chronic Diseases of the Chest, Philadelphia General Hospital, Phila., Pa.)

In a group of twenty-seven autopsied Negroes with sickle cell anemia 82 per cent showed pleural adhesions and 30 per cent had tuberculosis. In a control series of 130 autopsied Negroes only 44 per cent showed pleural adhesions and 9 per cent had tuberculosis. In one specimen vessels within tuberculous lung tissue were packed with sickled red cells whereas adjacent areas of normal lung tissue showed red cells of normal shape. Of 150 tuberculous Negroes tested for the sickling trait, 12.6 per cent were sicklers whereas of 150 non-tuberculous Negroes 5.2 per cent were sicklers. Among the tuberculous Negroes 78 per cent of the nineteen sicklers showed an exudative type of pulmonary tuberculosis whereas only 38 per cent of the 131 non-sicklers showed exudative tuberculosis. One of the sicklers had a pneumonectomy and the microscopic lung sections showed that the small vessels were packed with sickled red cells. These findings suggest that Negroes with the sickle cell trait are more prone to develop pulmonary tuberculosis (usually of the exudative type) than Negroes without the trait. The sickling phenomenon is a factor in the response of some Negroes to tuberculous infection. Possible explanations for this are discussed.

AUREOMYCIN AND EXPERIMENTAL HEMORRHAGIC SHOCK. *A. H. Williams, M.D., and R. W. Clarke, M.D.** (From the Army Medical Service Graduate School, Walter Reed Army Medical Center, Washington, D. C.)

Recently, in experimental hemorrhagic shock, Fine and co-workers found that oral neo- and aureomycin (1) delayed the onset of peripheral vascular collapse and (2) markedly reduced the incidence of irreversibility following reinfusion of the blood withdrawn. The results were attributed to suppression of enteric bacteria. Because such a mechanism might affect all types of shock, it was necessary to evaluate its role as a preliminary step. In contrast to the method employed by Fine's group our dogs were subjected to hemorrhagic shock by a technic which does not depend upon regulation of levels of arterial pressure (W. W. Walcott, 1945). The criteria used to evaluate the antibiotic effect were the patterns of circulatory responses and the survival time after the initial bleeding. Animals of comparable size were anesthetized with nembutal and measurements made of heart rate, blood pressure, respiratory rate and rectal temperature at fifteen- to thirty-minute intervals. Although the variations were noted in individual dogs, including variations in bleeding

volume, no significant physiologic differences were attributable to aureomycin in the doses employed nor were findings at autopsy altered.

OVALOCYTOSIS WITH HYPERSPLENISM: REPORT OF TWO CASES AND OBSERVATIONS ON THE PATHOGENESIS OF THE HYPERSPLENISM. *H. E. Wilson, M.D. and M. J. Long, M.D.** (From the Northwestern University, Chicago, Ill.)

Two of five siblings were found to have ovalocytosis. The first, a sixty-three year old female, entered in an attack of acute cholecystitis with a history of long-standing anemia. Significant findings on admission were fever, icterus, moderate hepatomegaly and splenomegaly, ovalocytosis with anemia and a relative leucopenia. Bone marrow was hyperplastic in all elements. After subsidence of fever and jaundice an adrenalin test produced marked splenic contraction concurrent with significant increases in all of the peripheral blood cell elements. Erythrocyte osmotic fragility was normal, Coombs' test negative. A gallbladder full of pigment stones and a 300 gm. spleen showing fibrosis and hemosiderosis were removed. Postoperatively, all of the peripheral blood cells rose to high normal levels. Coincident with the recovery from the pancytopenia was the appearance of increasing numbers of ovalocytic and spherocytic microcytes. Erythrocyte mechanical fragility was greatly increased, the osmotic fragility moderately increased. This patient's fifty-eight year old brother shows splenomegaly, anemia and a uniform ovalocytosis similar to that observed in his sister preoperatively. Mechanical fragility is slightly but significantly increased. Comparison of these two cases and the effects of splenectomy demonstrate the importance of red cell shape and size on mechanical fragility and on splenic sequestration. These observations support Bjorkman's experimental work on splenic filtration and circulation.

HUMAN STUDIES WITH ACTX, A HIGH-POTENCY CORTICOTROPIN SUB-TYPE CHARACTERIZED BY A HIGH RATIO OF INTRAMUSCULAR TO INTRAVENOUS ACTIVITY. *W. Q. Wolfson, M.D., W. D. Robinson, M.D., J. R. Quinn, M.D.* and I. F. Duff, M.D.* (From the Rackham Arthritis Research Unit, University of Michigan Medical School, Ann Arbor, Mich.)

ACTX is a high-potency corticotropin prepared by chromatographic fractionation. When given intramuscularly each U.S.P. unit of ACTX appears metabolically and therapeutically equivalent to approximately 3 U.S.P. units of intramuscular U.S.P. corticotropin (ACTH).

ACTX in Light Gelatin (ACTX-LG) q.6.h. i.m.: Four patients receiving 2.5 to 5.0 units of ACTX-LG q.6.h. consistently showed circulating eosinophils below 10 per cent of pre-treatment levels. Under assay conditions in one subject 2.5 units of ACTX-LG q.6.h. produced metabolic effects greater than those of q.6.h. administration of 12.5 units of two aqueous ACTH preparations.

ACTX in Heavy Gelatin (ACTX-HG) once daily: in initiating and maintaining remissions in comparable patients, effectiveness of ACTX-HG averaged better than three times that of ACTH in heavy gelatin. Twenty-four hours after receiving 35 to 40 unit doses of ACTX-HG medium eosinophil count in twelve subjects was 0 per cu. mm., a result not duplicated by 100 units of long-acting ACTH preparations. Under assay conditions in one subject ACTX-HG preparations from two different manufacturers were closely similar. Distinctive labelling and dosage instructions for ACTX appear advisable. Since intermittent intramuscular ACTX-LG approaches the effectiveness of intravenous ACTH infusions, ACTX probably undergoes less extravascular inactivation than ACTH.

AORTIC STENOSIS MASKING AS CHRONIC COR PULMONALE. *J. Zatuchni, M.D.* and L. A. Soloff, M.D.* (From the Dept. of Medicine, Temple University Hospital and School of Medicine, Philadelphia, Pa.)

The postmortem discovery of aortic stenosis in an individual free of cardiac murmurs who had presented for years the clinical syndrome of chronic cor pulmonale prompted an investigation of the circulatory hemodynamics of aortic stenosis. Nine consecutive subjects were studied. The right heart circulation time was prolonged in all. The venous pressure may be elevated. The aortic murmur may or may not be characteristic and with failure may disappear entirely. Only with failure is the left heart time prolonged and even then it is disproportionately slow compared to the right. With increasing venous hypertension an absent or insignificant aortic murmur, an emphysematous chest so frequent in the elderly and pulmonary symptoms, the picture of chronic cor pulmonale is

produced. Unexplained electrocardiographic or radiologic evidence of left ventricular enlargement should arouse suspicion of the presence of aortic stenosis. Conversely, the right heart time may be of value in assessing the significance of an aortic systolic murmur.

RELATIONSHIP OF SODIUM, POTASSIUM AND CHLORIDE OF THE BLOOD TO EDEMA FLUID AND URINE ELECTROLYTES IN INTRACTABLE CARDIAC FAILURE. *J. Zatuchni, M.D.* and L. A. Soloff, M.D.* (From the Dept. of Medicine, Temple University Hospital and Medical School, Phila., Pa.)

An individual with intractable cardiac failure and with pre-existing normally functioning kidneys died on the thirty-ninth day of hospitalization. During this time his diet was fairly uniform and constant for sodium and potassium. Daily records were made of the weight and fluid balance, of the concentration of sodium, potassium and chloride of plasma and edema fluid and of the total output of these ions in the urine. The effect was noted on these determinations of (1) no medication, (2) digitoxin, (3) hypertonic saline, (4) mercurials and (5) potassium acetate. In the untreated state the blood sodium was significantly higher than that of the edema fluid. This relationship could be temporarily reversed by mercurials that caused a sharp increase in urinary sodium and chloride. Oral potassium was excreted almost quantitatively in the urine. Hypertonic saline and digitoxin were without appreciable effect. The individual variability of the manifestation of cardiac failure and significance of the gradient of sodium between plasma and edema fluid are discussed.

INSIGNIFICANT LOSS OF INSULIN SENSITIVITY IN PATIENTS RECEIVING ACTH. *H. J. Zimmerman, M.D., A. E. Parrish, M.D. and L. K. Alpert, M.D.* (From the Veterans Administration Hospitals, Omaha, Nebr., and Washington, D. C.)

It has been suggested that insulin-insensitive diabetes mellitus is due to excess insulin antagonists. Our previous studies have shown that the administration of desoxycorticosterone acetate to patients with insulin insensitive diabetes mellitus is followed by an apparent increase in responsiveness to insulin. It was postulated that the steroid inhibited the release of contra-insulin factors possibly from the pituitary or adrenal glands. Sayers and his group have postulated that increased sensitivity of rats to insulin induced by desoxycorticosterone is due to inhibition of ACTH release. To test the validity of this postulate ACTH was administered to a group of twelve non-diabetic patients and the effect on the insulin responsiveness determined. Insulin responsiveness was determined by the Himsworth glucose-insulin-tolerance test before and during the administration of ACTH in doses varying from 40 to 100 mg. daily. In some of the patients a standard insulin tolerance was performed as well. No patient showed a marked decrease in responsiveness to insulin and in most there was little if any decrease. This was true not only in the glucose-insulin-tolerance test but when measured by the standard insulin tolerance test as well. Glucose tolerance showed mild impairment in all patients studied. Comparison of the distinct increase in sensitivity to insulin in insulin-insensitive diabetics receiving desoxycorticosterone with the negligible effect of full doses of ACTH in decreasing insulin responsiveness suggests that the desoxycorticosterone effect previously noted is not due to inhibition of the production and release of ACTH.

INEFFECTIVENESS OF DESOXYCORTICOSTERONE ACETATE IN INHIBITING THE EVIDENCE OF STRESS IN PATIENTS RECEIVING INSULIN-SHOCK THERAPY. *H. J. Zimmerman, M.D., J. R. Walsh, M.D.,* R. B. Johnson, M.D.* and F. Humoller, M.D.** (From the Veterans Administration Hospital, Omaha, Nebr.)

The increase in insulin sensitivity occurring in rats after administration of desoxycorticosterone has been attributed to the demonstrated ability of this steroid to inhibit the output of ACTH. An increase in sensitivity to insulin has also been demonstrated in insulin-insensitive human diabetes mellitus after the administration of desoxycorticosterone acetate. In an attempt to evaluate the role of adrenocortical inhibition in this phenomenon, studies were made of twelve psychiatric patients receiving insulin-shock treatment. Total eosinophil counts were obtained initially and five hours after the administration of insulin. Glucose and glucose-insulin-tolerance studies (Himsworth) were made before the initiation of insulin shock treatment and at intervals of two weeks thereafter. Alternate patients were given 10 mg. of desoxycorticosterone daily intramuscularly. The changes in glucose-insulin-tolerance and the degree of eosinopenia produced by insulin shock were compared in the patients receiving DCA and in the control group. The majority showed a

profound drop in the total eosinophil level. Eighty-five per cent of the determinations in the control group showed a drop of more than 50 per cent while 70 per cent of the determinations in the DCA treated patients showed a significant eosinopenia with insulin shock. DCA was ineffective in inhibiting the eosinopenia developing after large doses of insulin but was suggestively effective in inhibiting the eosinopenia during the first week of insulin administration when doses were relatively small. In both the DCA treated patients and the control group a loss of glucose tolerance and a mild loss of insulin tolerance developed. No significant difference could be noted between the two groups of patients. It seems, therefore, that the severe stress of large doses of insulin cannot be inhibited by desoxycorticosterone.

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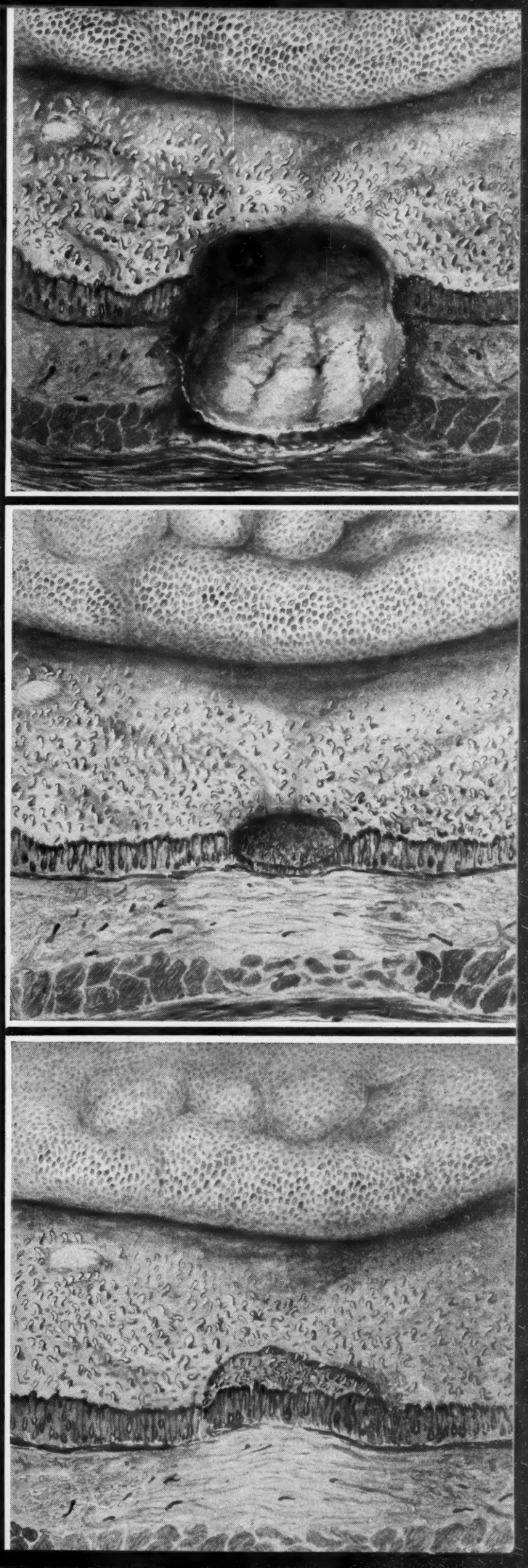
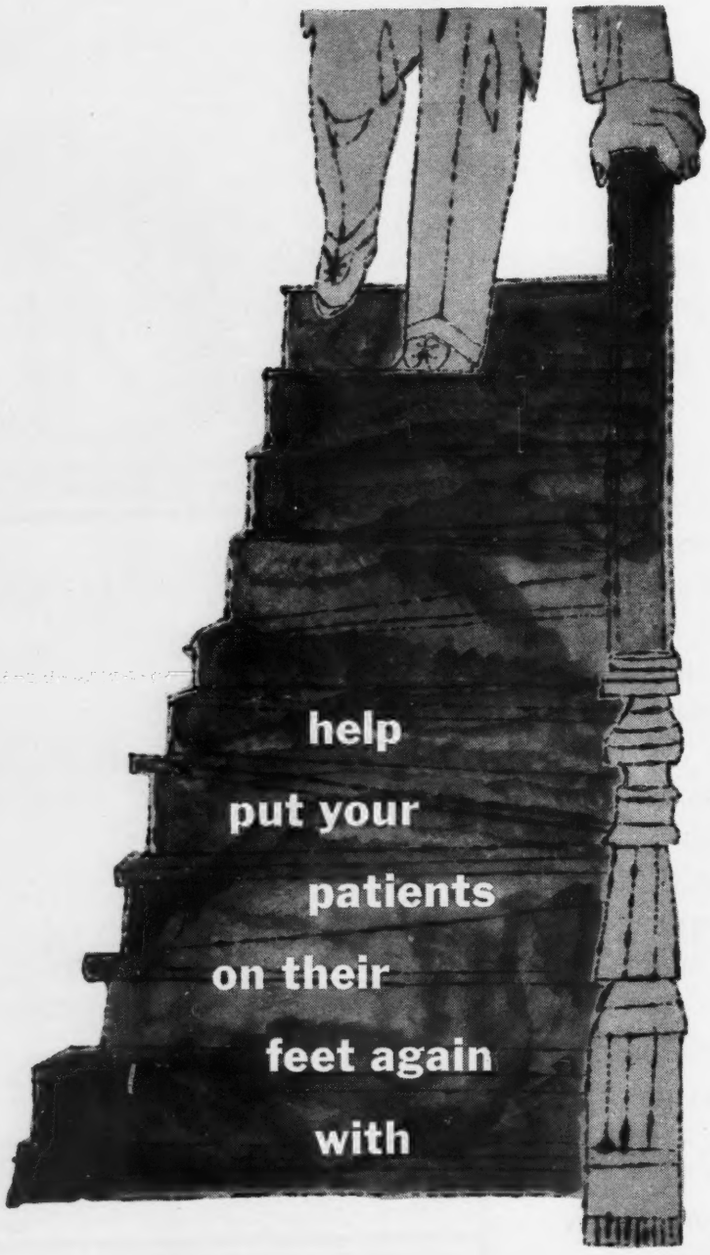


Top—Section through duodenal bulb just distal to pylorus through center of ulcer crater.

Center—Healing ulcer with scar tissue and regeneration of tissue layers.

Bottom—Healed ulcer with restoration of mucosa.



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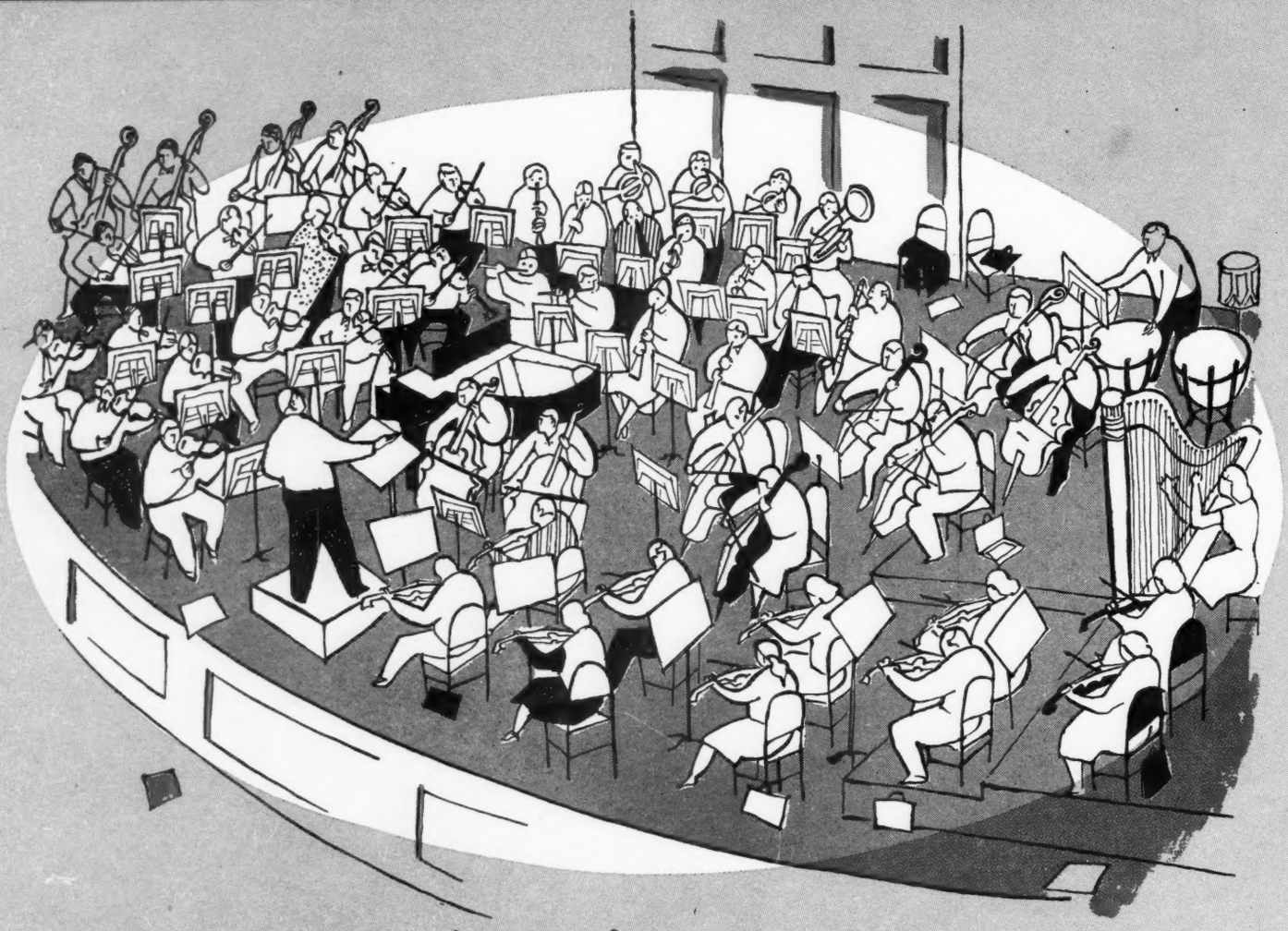

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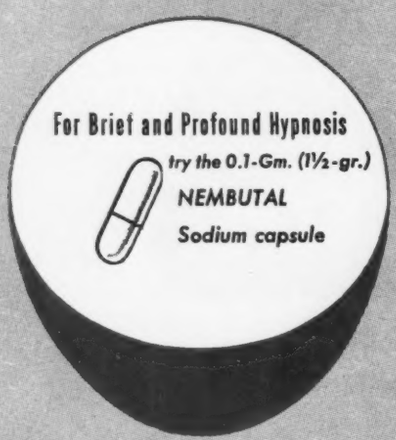

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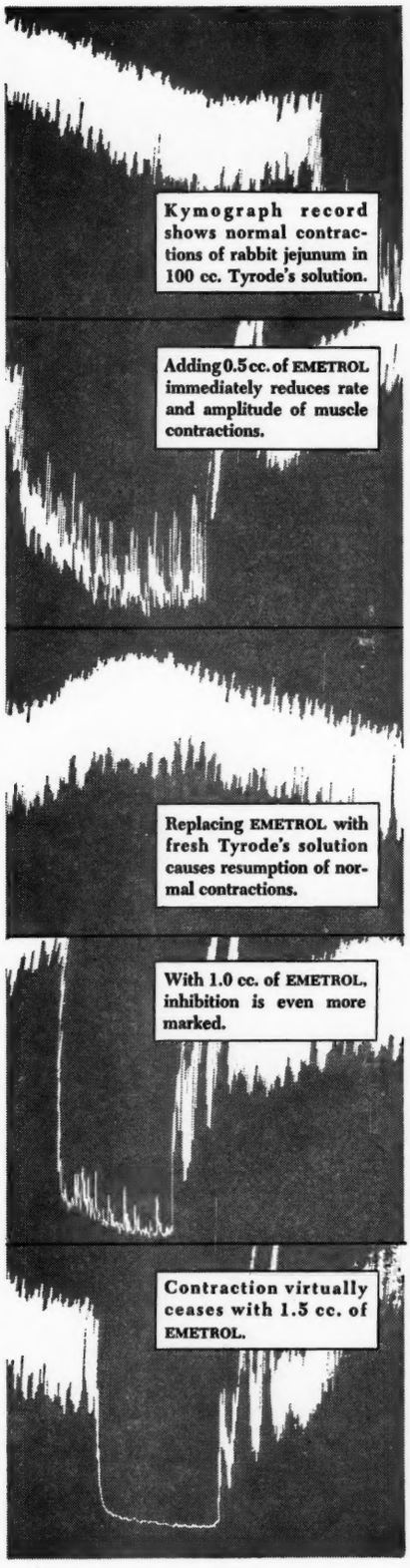

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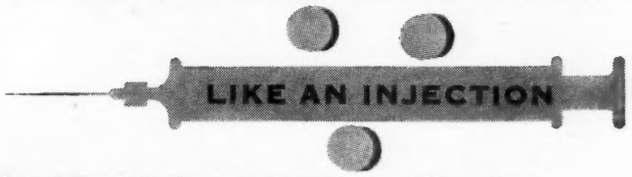

1. Moyer, J. H., and Handley, C. A.: Federation Proc. *11*:378, 1952.
2. Greiner, T.; Gold, H.; Warshaw, L.; Palumbo, F.; Weaver, J.; Mathes, S., and Marsh, R.: Federation Proc. *11*:352, 1952.
3. Goldman, B. R., and Steigmann, F.: J. Lab. & Clin. Med. *40*:803, 1952.

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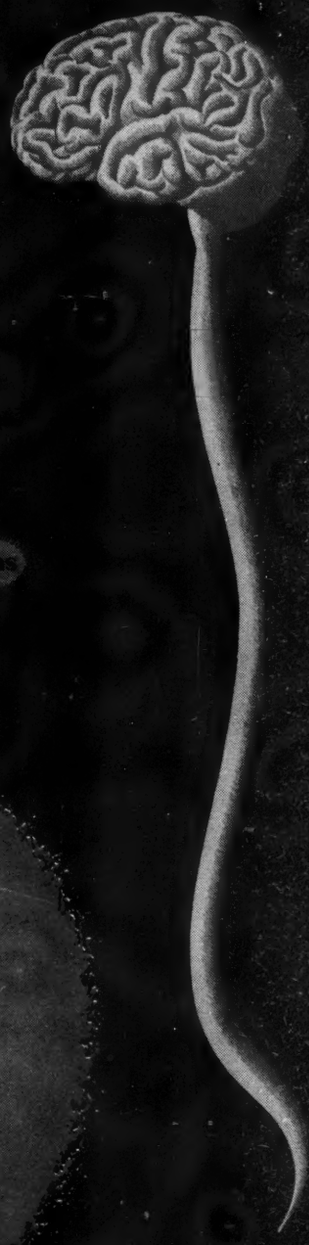

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*Hermann, I. F., and Smith, R. T.: JL. Lancet 71:271 (July), 1951.

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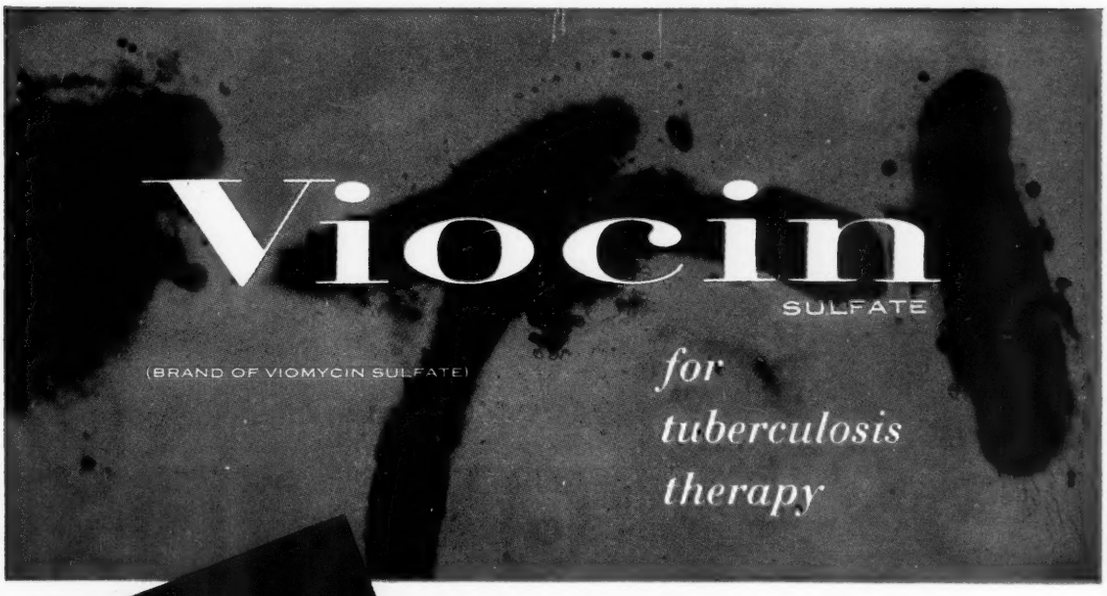

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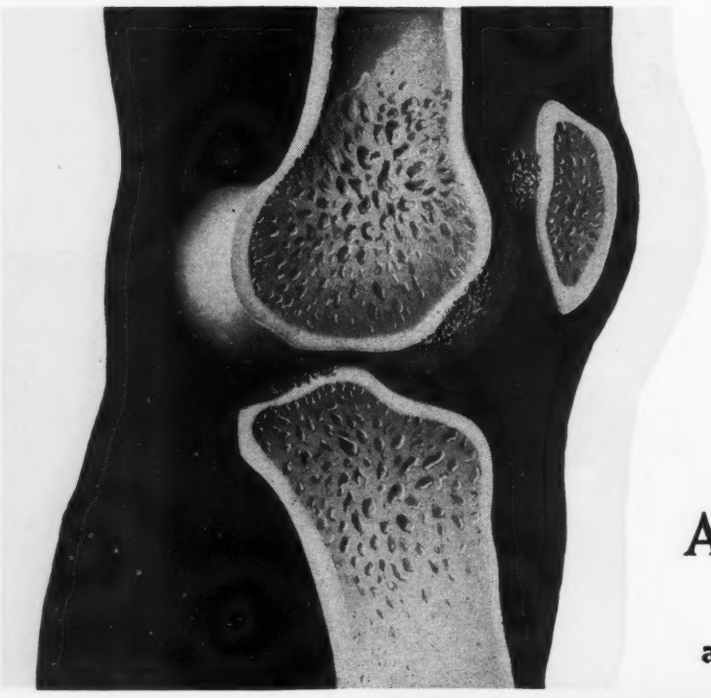

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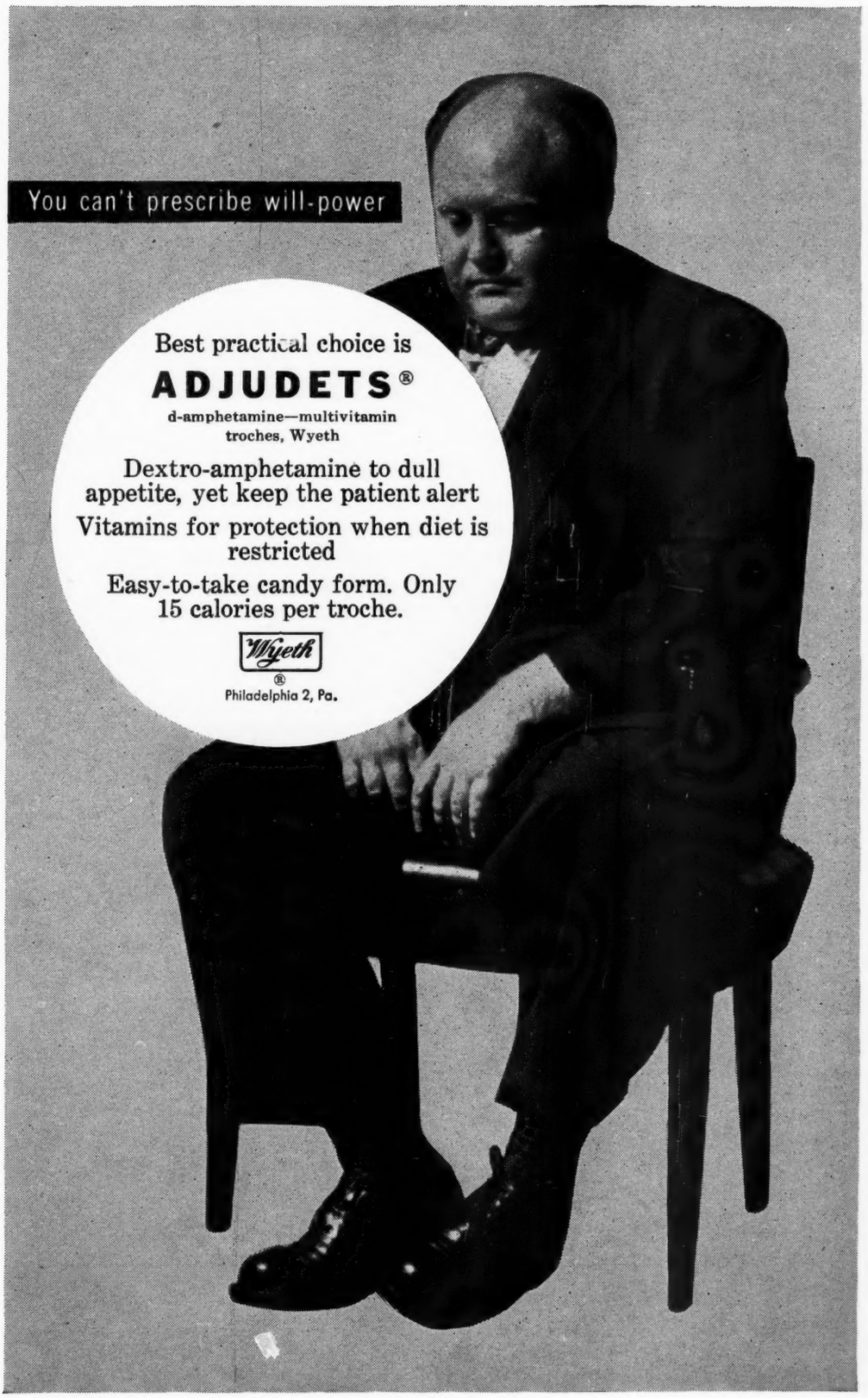
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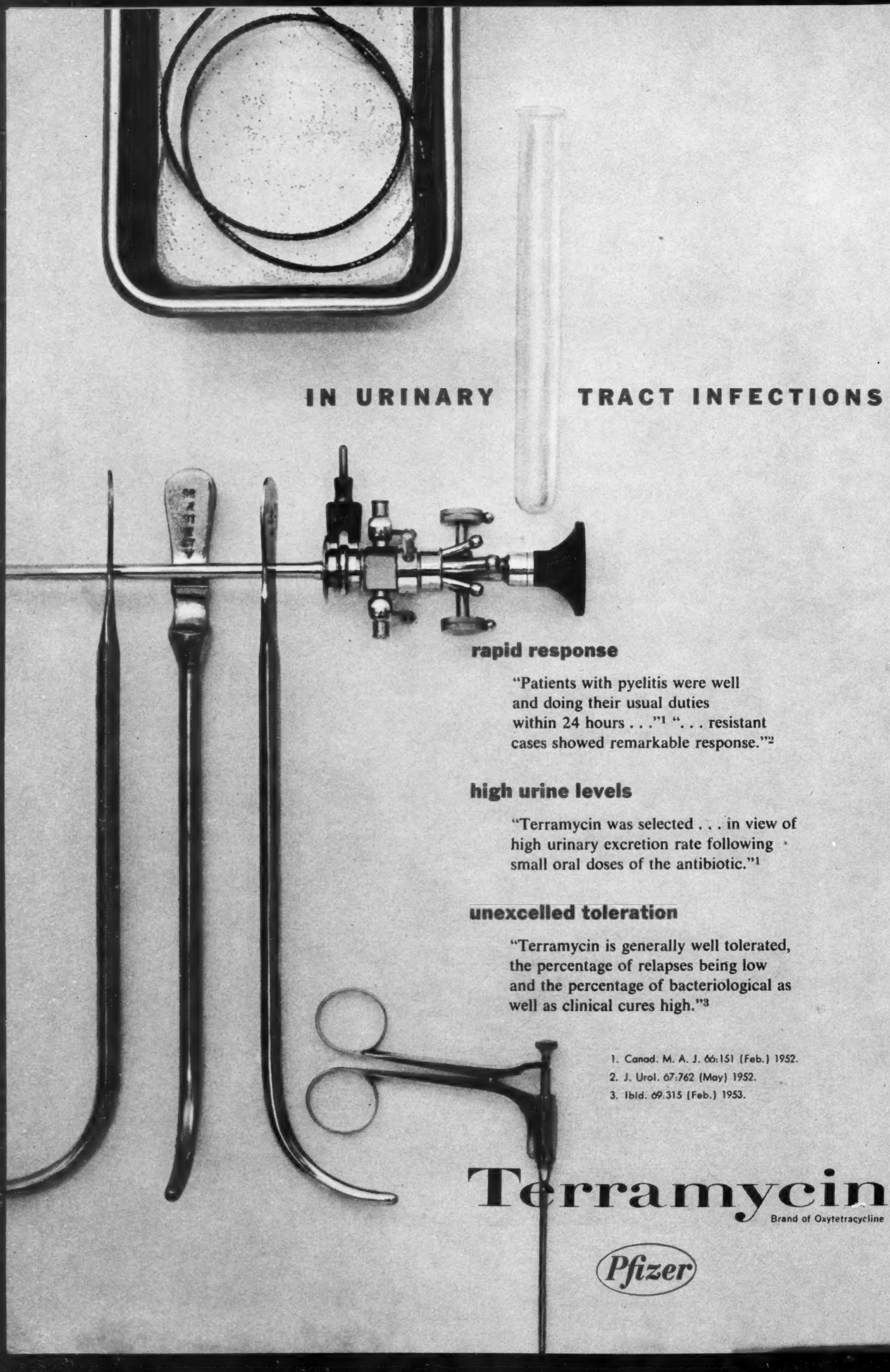

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1. Canad. M. A. J. 66:151 (Feb.) 1952.
2. J. Urol. 67:762 (May) 1952.
3. Ibid. 69:315 (Feb.) 1953.

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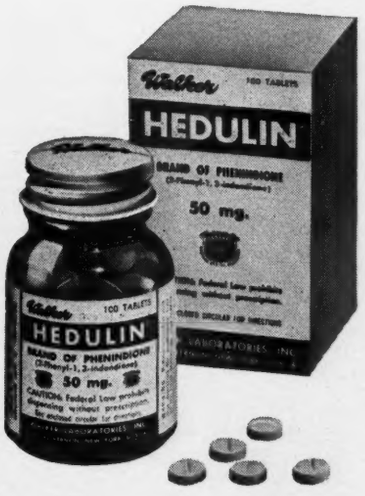
DOSAGE: 4 to 6 tablets (200 to 300 mg.) initially, half in the morning and half at night; maintenance dosage (on basis of prothrombin determinations daily for first three days), 50 to 100 mg. (av. 75 mg.) daily, divided as above.

Already available in the pharmacies of all major hospitals or on prescription at retail pharmacies throughout the country. Specify **HEDULIN** (Walker)—original bottles of 100 and 1000 50-mg. scored tablets.



Complete literature to physicians on request

Walker

WALKER LABORATORIES, INC., MOUNT VERNON, N. Y.

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NEW!

"Bemotinic" Liquid

in the common anemias

Unequalled for taste
Unusually palatable. No need to dilute or mask . . . just a pleasantly rich orange flavor, with no aftertaste.

Effective action
Provides essential factors for maximal hemopoietic and clinical response . . . includes a B_1 potentiator.

Simple administration
Directly from the spoon because of high degree of palatability . . . smooth, nonviscous, easy-pouring.

Palatable Orange Flavor—Nonalcoholic

Each teaspoonful (5 cc.) contains:

Ferric ammonium citrate	200.0 mg.
Vitamin B_{12} U.S.P. (crystalline)	4.0 mcg.
Extractive as obtained from of fresh gastric tissue	450.0 mg.
Folic acid	0.33 mg.
Thiamine HCl (B_1)	1.5 mg.
Riboflavin (B_2)	1.0 mg.
Pyridoxine HCl (B_6)	0.2 mg.

Suggested dosage:
Adults: 1 to 2 teaspoonfuls
Children: ½ to 1 teaspoonful
Three times daily, or more as required.
No. 940 Supplied in bottles of 16 fluidounces and 1 gallon.

5302

Ayerst, McKenna & Harrison Limited
New York, N. Y. • Montreal, Canada

Upjohn

diarrhea...

Kaopectate

Trademark Reg. U.S. Pat. Off.

Each fluidounce contains:

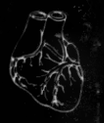
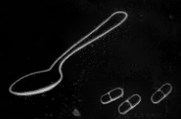
Kaolin . . . . . 90 grs.

Pectin . . . . . 2 grs.

in an aromatized and carminative vehicle

Available in bottles of 10 oz. and 1 gallon

The Upjohn Company, Kalamazoo, Michigan

condition	 *incidence of liver dysfunction*	 *incidence of blood lipid abnormalities*	 *suggested therapy*
obesity	frequent + + +	frequent + +	Methischol plus balanced low calorie diet.
diabetes	frequent + + + +	frequent + + +	Methischol as adjunct to diet. Insulin as necessary.
atherosclerosis	frequent + + +	frequent + + +	Methischol and high protein, low fat diet.
coronary disease	frequent + + +	frequent + + + +	Methischol as adjunct to high protein, low fat diet and specific therapy.
alcoholism	frequent + + +	frequent + +	Methischol plus high protein diet.

methischol

the complete lipotropic therapy

...because it provides vitamin B_{12} and liver fractions in addition to choline, methionine and inositol.

...helps normalize liver function, increase phospholipid turnover, reduce fatty deposits, and stimulate regeneration of new liver cells...

...helps reduce elevated cholesterol levels and chylomicron ratios towards the normal, and aids in achieving normal fat metabolism.

now— higher B_{12}

the suggested daily therapeutic dose of 9 capsules or 3 tablespoonfuls of Methischol provides:

Choline Dihydrogen Citrate*	2.5 Gm.
dl, Methionine	1.0 Gm.
Inositol	0.75 Gm.
Vitamin B_{12}	18 mcg.
Liver Concentrate and Desiccated Liver**	0.78 Gm.

*Present in syrup as 1.15 Gm. Choline Chloride.
**Present in syrup as 1.2 Gm. Liver Concentrate

for samples and detailed literature write

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April, 1953

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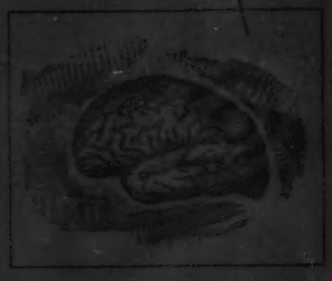
three new agents in the control of hypertension

Complete information can be obtained by writing to the Medical Service Division, Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

Esomid®

chloride (hexamethonium chloride Ciba), a potent oral hypotensive agent, may be particularly valuable in those patients with severe hypertension which has failed to respond to Apresoline. Esomid acts as a *ganglionic blocker*, inhibiting the transmission of impulses through all autonomic ganglia.



Apresoline®

hydrochloride (hydralazine hydrochloride Ciba), an agent of choice (for use) in the treatment of hypertension. This orally effective antihypertensive is believed to act *centrally* to produce a gradual, sustained decrease in blood pressure while increasing blood flow through the kidneys.

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